Dissertation on

A STUDY TO ANALYSE "POOR POSTNATAL WEIGHT GAIN" AS ONE OF THE PREDICTORS FOR "SEVERE FORM OF RETINOPATHY OF PREMATURITY"

Submitted in partial fulfillment of requirements of

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The Tamilnadu Dr.M.G.R. Medical University

CHENNAI, TAMILNADU

APRIL, 2017

CERTIFICATE

This is to certify that this dissertation entitled **A STUDY TO ANALYSE "POOR POSTNATAL WEIGHT GAIN" AS ONE OF THE PREDICTORS FOR "SEVERE FORM OF RETINOPATHY OF PREMATURITY"** is a bonafide record of research work done by **Dr. SOUNDHARYA S,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

She has submitted this in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, for the award of Master of Surgery Degree Branch III (Ophthalmology), under our guidance and supervision during the academic years 2014-2017.

Dr. P. THIYAGARAJAN, M.S, D.O.,

HOD and Professor of Ophthalmology,

GRH, Madurai Medical College,

Madurai.

Dr. M. R. VAIRAMUTHU RAJU, M.D

The Dean,

GRH, Madurai Medical College,

Madurai.

CERTIFICATE FROM GUIDE

This is to certify that this dissertation entitled **A STUDY TO ANALYSE "POOR POSTNATAL WEIGHT GAIN" AS ONE OF THE PREDICTORS FOR "SEVERE FORM OF RETINOPATHY OF PREMATURITY"** is a bonafide record of research work done by **Dr. SOUNDHARYA S,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

Dr. N. PARVATHASUNDARI, M.S, D.O.,

Senior Assistant Professor of Ophthalmology,

GRH, Madurai Medical College,

Madurai.

Dr. S. V. CHANDRAKUMAR, M.S, DO.,

Associate Professor of Ophthalmology,

GRH, Madurai Medical College,

Madurai.

DECLARATION

I, **Dr. SOUNDHARYA S** hereby solemnly declare that, this dissertation titled **A STUDY TO ANALYSE "POOR POSTNATAL WEIGHT GAIN" AS ONE OF THE PREDICTORS FOR "SEVERE FORM OF RETINOPATHY OF PREMATURITY"** was done by me.

I also declare that this bonafide work / a part of this work was not submitted by me / anyone else, for any award, for Degree / Diploma to any other University / Board either in India / abroad. This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery degree Branch -III (Ophthalmology) to be held in April 2017.

Place: Madurai (Dr. SOUNDHARYA S)

Date:

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ANNEXURES

PART I

INTRODUCTION

Retinopathy of Prematurity (ROP) is a disease affecting the retina of premature infants.[1]

It is one of the leading causes of preventable childhood blindness in India. In our country, ROP incidence is between 38 – 51.9 % in low birth weight babies. With improved neonatal care and better survival rate of preterm infants, ROP incidence in our country is on the increasing trend.[2-4]

The fundamental pathological process underlying ROP stems from incompletely vascularised peripheral retina at birth in preterm babies.[5]

After birth, ROP evolves slowly over 4-5 weeks and this gives us a small window of opportunity for predicting the development of severe ROP and timely interventions to improve visual outcome thereby avoiding irreversible blindness.[5]

ROP incidence increases with decreasing Gestational Age (GA) and Birth Weight (BW), however not in all preterm babies. So, there might be other fetal and or maternal risk factors influencing the ROP development. These factors may protect or increase the probability of development of ROP.[6,7]

According to revised ET-ROP study, approximately 8% screened babies require treatment based on current ROP screening guidelines.[8] In more than 90% of babies ROP is either regressing or never developing.

Although current ablation treatment reduces the incidence of blindness in babies with severe stages of ROP, these babies still have poor visual outcome and there exists significant impact of the disease on development of eye and vision.

Recent studies showed that one of the strongest predictors of "severe ROP" is "poor postnatal weight gain" in early postnatal period.[9,10] However current screening protocols does not include this risk factor as a predictor for the development of ROP.

Identifying a modifiable postnatal risk factor like poor postnatal weight gain by simple serial postnatal weight measurements helps in identification of premature babies at risk for developing severe ROP more specifically, thereby avoiding unnecessary stressful examination to babies not at risk, and also predicting the disease earlier before it is diagnosed by regular ocular examination that helps in early intervention and prevention of severe vision loss and unfavourable outcome.

HISTORY

Terry was the first to report it in 1942 in American journal of Ophthalmology.[11] Dr.Harry Messenger coined the term Retrolental fibroplasia, by which ROP would be known for 40 more years. He related it to persistent hyaloid artery and tunica vasculosa lentis and embryonic connective tissue growth behind the lens.[12]

Owens and Owens first reported the case series of infants with Retrolental fibroplasia and reported that pathogenesis was not related to congenital abnormalities of hyaloid system and it developed postnatally.[13]

In 1950s, relationship between ROP and supplemental oxygen was discovered. Multicentre randomized clinical trial, National Cooperative Study proved the correlation to oxygen supplementation which led to reduction of O_2 supplementation in neonatal care unit that led to reduced ROP incidence. But, this led to increased mortality and morbidity of premature infants.[14,15]

In 1970s, neonatal care unit started using arterial blood gas analysis that enabled pediatricians to titrate oxygen concentration of incubator to meet individual oxygen needs and led to decreased incidence of ROP.[16] Morbidity decreased due to rigid oxygen curtailment and optimized oxygen concentration.

In 1980 ROP began to rise due to more survival rate of preterm babies with advancement in neonatal care.

INCIDENCE AND PREVALENCE

In India, ROP incidence is between 38 – 51.9 % in low birth weight babies. In our country, annual live births is around 26 million, of which approximately 8.7% are with BW of <2000 grams. This shows that almost 2 million newborns are at risk for ROP.[17]

"Vision 2020 programme" of World Health Organization's has found ROP as one of the significant cause of blindness in middle and high income countries.

Incidence of ROP in gestational age of 24-27 weeks is 89 %. As the gestational age increase, ROP incidence decreases.

ROP incidence in BW of <750gms is 90%. As the BW increases, ROP incidence decreases. ROP can be seen in 80 to 90 % of low birth weight babies exposed to oxygen therapy.

This table shows ROP incidence and severity in premature babies with birth weight ≤1,251 g[18–21]

STUDIES	No.of babies	Any ROP (%)	Prethreshold ROP (%)	Threshold ROP (%)
CRYO-ROP STUDY	4,099	66	18	6
LIGHT-ROP STUDY	361	70	14	5
ET-ROP STUDY	6,998	68		

This table shows the severe ROP incidence among premature babies in CRYO-ROP study and ET-ROP study[18-21]

STUDIES	Patients	Prethreshold ROP (%)	Plus (%)	Zone I ROP (%)
CRYO-ROP STUDY	2,699	27	17	2
ETROP-ROP STUDY	2,320	37	24	9

Blind school survey reported that in African countries, severe visual impairment due to ROP was zero percent and in Cuba it was 38.6%. Due to poor neonatal services the low birth weight babies do not survive to develop ROP in African countries.

Present ROP epidemic is of concern mostly with developing countries. The reason for this is premature babies surviving with more intensive neonatal care units; neonatal services have not reached the adequate level of care where the infants are unmonitored supplement of oxygen.

NORMAL RETINAL VASCULOGENESIS

The vascular supply of retina consists of:

1. Choroid vessels that underlie the retina.

2. Retinal vessels that serve the inner retina.

Brain and retinal development of the fetus are intimately connected.

Vision begins – around 28 weeks of GA and

Visual responses measureable – around 32 weeks of GA.

Normal retinal vascular development starts at the optic disc at about 16 weeks of gestation by vasculogenesis and then proceeds to reach nasal ora serrata at about 36 weeks of GA and temporal ora serrata at about 40 weeks of GA by angiogenesis.[22-26]

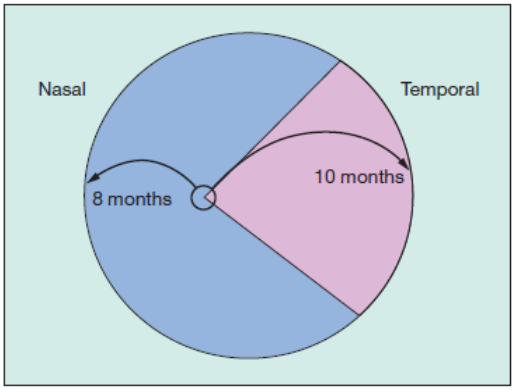
Vascular development of retina is by angiogenesis, arteriogenesis and vascularisation.

Angiogenesis – Endothelial lined blood vessel formation

Arteriogenesis – Smooth muscle cells are added to endothelial cells to produce intact arterioles.

Vascularisation – New arterialization of a tissue. Combination of these three is termed vasculogenesis.

Vasculogenesis is the denovo development of normal vasculature, involves the proliferation, differentiation, and organization of angioblasts. Circulating angioblasts in the area surrounding the optic nerve develops early retinal vessels.[27,28]



Vessels reach nasal ora serrata first because nasal ora serrata is shorter distance from disc compared to temporal ora serrata.

Before 28 weeks GA, outer segments of photoreceptors are not active, so metabolic demand of the retina is less and hence need for nutrition is low. At this time, entire retina is supplied by diffusion from choroidal circulation and development of choroidal vasculature completes by 22 weeks of gestation.

At 28-32 weeks, vision begins and photoreceptor activates, metabolic demand increases and need for more blood supply but little change occurs in the choroidal vasculature. As a result of this, retina needs its own vascular supply to meet its metabolic demands.[29-32]

Retinal vascular development occurs in a relatively hypoxic environment in uterus where average PaO_2 is 25-35mmHg, supported by fetal haemoglobin and lower metabolic demands.

The retinal vasculature comprises two laminar layers, the primary superficial layer and ganglion cell layer in deeper retina which are interconnected by fine capillaries.[37]

The formation of the primary vascular layer in the retina is associated with development of cells (astrocytes) in the nerve fibre region.

Astrocytes are glial cells that provides biochemical support to endothelial cells, helps to sense physiologic hypoxia and express VEGF.

VEGF is one of the important factors in vascular development and is associated with pathological angiogenesis. It creates a chemotactic gradient in extension of retinal angiogenesis to the peripheral ora serrata.

From the optic nerve astrocytes emerge and they migrate just ahead of the developing vasculature.

Astrocytes are present only in retina where retinal vasculature forms, and are restricted to the inner layer of retina that allows them to respond to hypoxia of the inner layers by expressing VEGF which is essential to induce the formation of the superficial layer of blood vessels.

Hyperoxia inhibits the formation of new blood vessel by down-regulating the VEGF expression of astrocyte. This down regulation may lead to a delay in the natural vascular development of retina.

Insulin like growth factor(IGF-1) is another important factor in retinal vascular development. IGF-1 through control of VEGF activation regulates the retinal vascular development.

Several studies showed the permissive role of IGF-1 in development of new blood vessel through control of VEGF activation.

Low levels of IGF-1 retards the vessel growth despite the presence of VEGF. Fetus gets IGF-1 from placenta and amniotic fluid.[33-36]

PATHOGENESIS OF ROP

When an infant is born prematurely, the retinal vascular development must occur in an altered environment, thereby creating the risk for development of ROP.

PHASES OF ROP:[38]

Phase 1: hyperoxia-vasocessation phase.

From birth to 30-32 weeks of postmenstrual age (PMA). It is associated with apparent delay in regression of hyaloidal circulation.

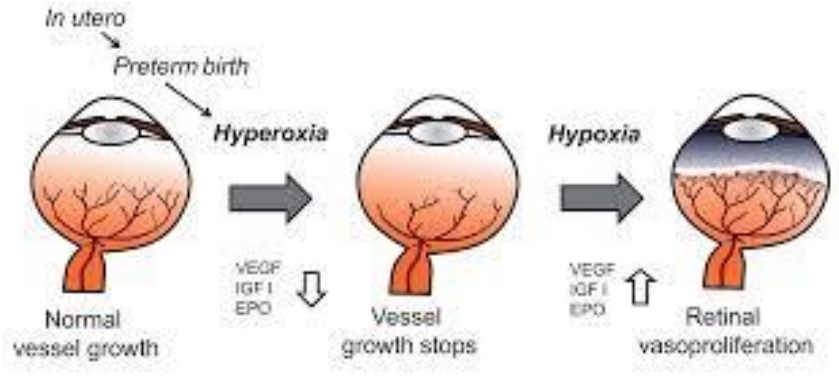
The infant's retina become hyperoxic (even in room air), leads to decline in VEGF level and vasculogenesis is stopped for a time at the junction of vascular retina and

avascular retina, thereby raising the risk for ROP development. Hyperoxia causes VEGF down regulation that leads to death of the endothelial cells.

Loss of newly developed capillaries will occur particularly if the infant was exposed to high oxygen at birth. Fluctuation in blood oxygen levels causes variation in concentration of VEGF, which is downregulated in hyperoxia and increased during hypoxia. Fluctuation in oxygen also leads to increased oxidative compounds, has a role in pathogenesis of ROP.

IGF-1, erythropoietin and other cytokines are altered by premature birth and change in environment can have a role in the delay of physiologic vascular growth of retina. Due to loss of IGF-1 provided by amniotic fluid and placenta, its level falls after birth and is also suppressed by poor nutrition and sepsis.

Preterm babies with prolonged “low serum IGF-1”and “poor postnatal weight gain” have high risk of ROP development. VEGF activation is suppressed by low IGF-1 level thereby decreasing the growth of retinal vasculature.



Phase 2: relative hypoxia - revascularisation phase.

Starts at around 32-34 weeks of PMA. Before 32 weeks of gestation, photoreceptors are not yet fully functional and metabolic demand of retina is low. As the retina matures, there is increase in metabolic demand and oxygen consumption creating a state of relative retinal hypoxia.

This increases the level of pro-angiogenic growth factors such as VEGF and erythropoietin leading to disordered growth of vessels into the vitreous. Overtime, postnatal levels of IGF-1 recover and reach a critical threshold, and triggering VEGF induced angiogenesis leading to development of ROP.

Phase 2 ROP does not proceed with a gradual transition from avascular to vascular retina, rather a demarcated ridge develops between the central vascularised and peripheral avascular retina. Histologically, this structure consists of mesenchymal and endothelial cells.

From this stage retinal vascular development may resume without significant disruption, or may lead to abnormal proliferation of retinal vessels into vitreous.

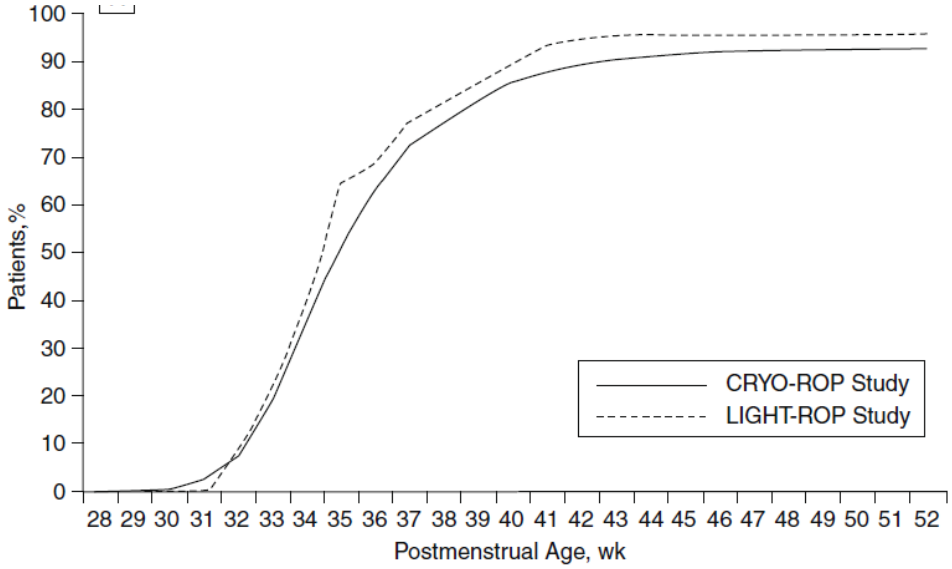
NATURAL HISTORY OF ROP

There occurs two forms of ROP. First is acute form followed by cicatricial or scarring/involutional forms.

Acute disease - between 30 and 45 weeks of PMA.

Cicatricial disease – starts as early as near term and continues for months post term.

Normal pattern of retinal vascularization was given by CRYO-ROP and LIGHT-ROP studies. Figure shows the zone III retinal vascularisation onset in no ROP babies. The two studies showed identical curves.



Vascularisation of nasal retina :

median age - 35 weeks of PMA

onset range - 31 to40 weeks of PMA.

The natural history of ROP gives details about risk factors, onset and progression and prognostic factors of ROP and is given by three multicenter trials i.e "CRYO-ROP study, LIGHT-ROP study and ET-ROP study". This includes infant specific data and retina specific data.

Infant specific data- BW, GA, gender, race, and multiple births.

Retina specific data - time of disease onset, stage, location, presence of plus disease, rate of progression as well as normal retinal vascularisation patterns.

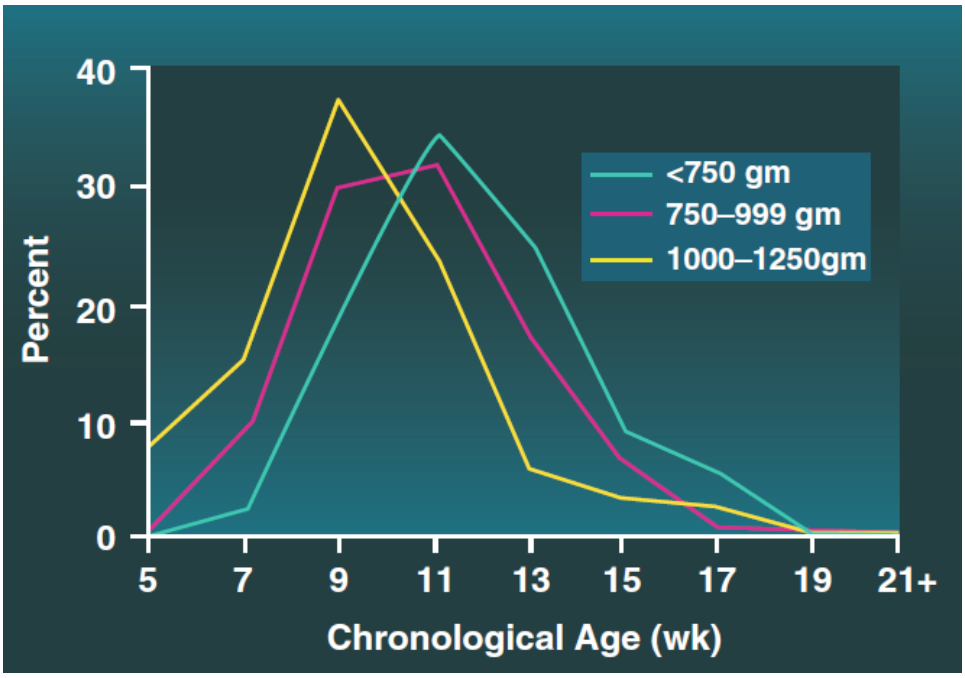
Incidence and severity of ROP is determined by GA and BW of infant specific data i.e. ROP incidence and severity increases with decreasing GA and BW.

In development of any stage of ROP, race did not seem to be a factor but it has a role in the severe ROP incidence. Compared to white, black infants had less incidence of plus disease, prethreshold ROP and threshold ROP.

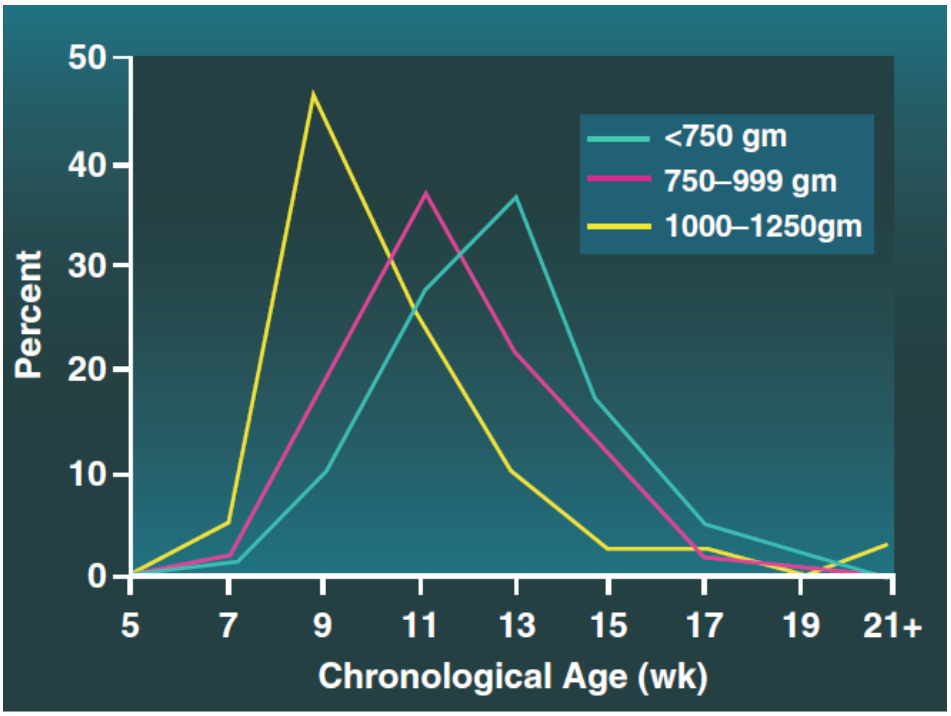
No difference in ROP incidence between males and females, but somewhat higher risk was found in multiple birth infants.

In 1991, from CRYO-ROP study, the most dramatic single natural history assessment was made by correlating prethreshold and threshold ROP onset with chronological age (CA) and postmenstrual age (PMA).[20]

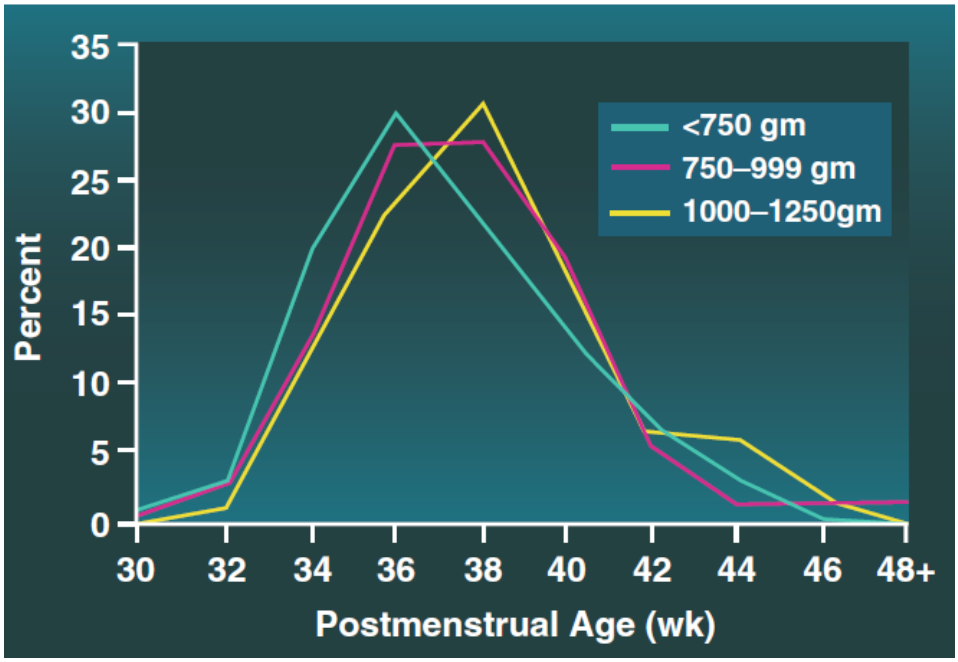
Graphical representation of onset of “prethreshold ROP” by BW and CA.[20]



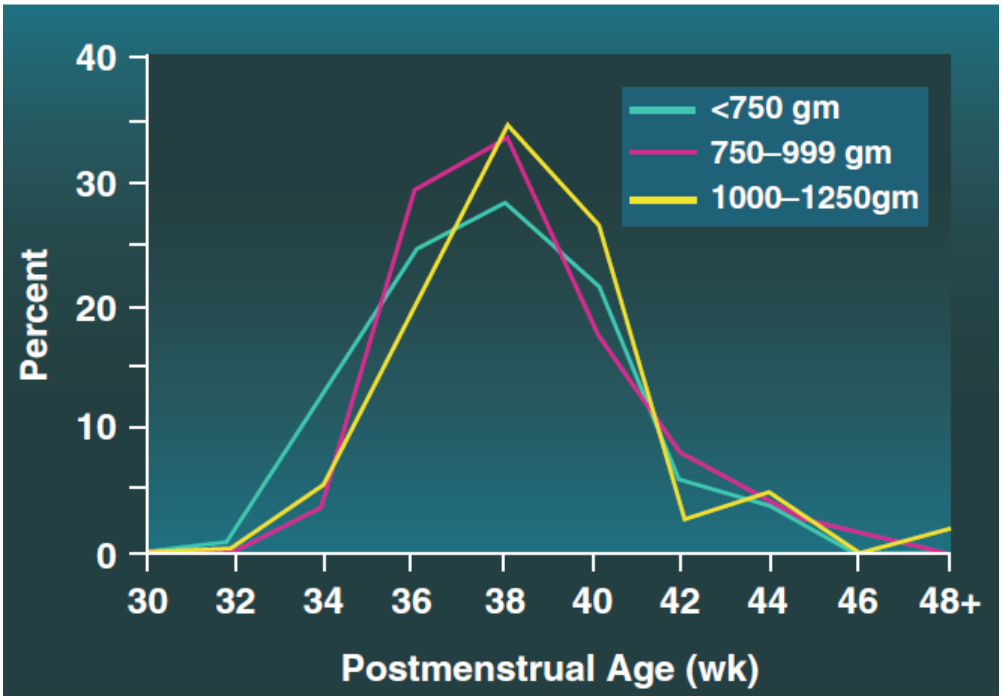
Graphical representation of onset of “threshold ROP” by BW and CA.[20]



Graphical representation of onset of “prethreshold ROP” by BW and PMA.[20]



Graphical representation of onset of “threshold ROP” by BW and PMA.[20]



Babies has been divided into birth weight quartiles in CRYO-ROP study as 1,000–1,250 g, 750–1,000 g, and less than 750. They found that the smallest and most premature babies had longer time duration with the longer period of environmental exposure to develop severe ROP from birth, which has notable role in ROP screening.

STUDIES	MEDIAN ONSET OF PRETHRESHOLD ROP (PMA)
CRYO-ROP study	36.1 weeks
ET-ROP study	36.1weeks

The "CRYO-ROP" study [39,40] found,

Major prognostic indicators:

ROP status,

The location by zone in which ROP develops, and

The presence of plus disease,

Minor prognostic indicators:

The circumferential extent of stage 3 disease, and

More difficult to assess rate of progression.

ET-ROP study confirmed the major importance of zone and plus disease. However, extent of stage 3 ROP by clock hours was not confirmed as an independent parameter in these studies. Presence of normal vascularisation in zone III and ROP in zone III has favourable prognosis but when zone II ROP is followed by zone III ROP negates this favorable prognosis.[41]

RISK FACTORS OF ROP

Although many causative factors for development of ROP have been proposed, however low BW, low GA at birth and O_2 supplementation have been consistently associated with ROP.

Role of oxygen: The significance of oxygen levels in development of ROP lies with choroidal circulation, in that it fails to autoregulate in response to altered O_2 tension. So in hyperoxic states, these vessels cannot constrict although the vessels of retina can constrict. As a result of this, movement of excess oxygen occurs from choroidal to retinal circulation which leads to constriction of retinal vessels to the point of obliteration.

Alternative theory, damage produced by reactive O_2 species particularly superoxide dismutase may outweigh the available defence mechanisms in the form of antioxidant enzymes such as α-tocopherol.

Hyperoxic states also interfere with spindle cell growth and maturation, leading to break in normal migration and retinal vasculogenesis. Chronic anaemia in mothers is found to be protective factor for development ROP in babies exposed to O_2 therapy in some studies.

Studies have demonstrated that continued supplementation of O_2 to babies who have developed "moderate ROP" does not decrease the ROP incidence, progression to "threshold ROP", although it was found that wide fluctuations in O_2 saturation levels may affect the development of ROP and progression.[42-44]

Today's modern neonatal intensive care units measures the oxygen saturation level and keeps it in controlled fashion thereby eliminating this risk.

Role of genetic factors: In the early 1990s, the hypothesis put forwarded was genetic factors may also influence the ROP development and was suggested by the variation noted between different ethnic groups.

This racial variation supports the role of genetic, socioeconomic or dietary factors in ROP development.

Recent clinical and experimental studies in monozygotic twins with genetic approach showed that, there exists a strong genetic predisposition for the development of ROP.[45,46] Studies showed three genes (Norrin, Frizzled 4, Lrp5) in Wnt signaling molecular pathways for development were mutated in some cases of advanced stage of ROP.[47-49] This explains the progression to severe stage of ROP occurs in some babies even with timely intervention whereas spontaneous regression occurs in other babies with similar ROP.

Multivariate analyses identified the following as independent risk factors for the ROP development.[38]

- low IGF-1,
- poor postnatal weight gain,
- hyperglycemia,
- blood transfusions,

- surfactant therapy and
- artificial ventilation for more than 7 days.

Other risk factors include

- systemic infections
- intraventricular hemorrhage
- bronchopulmonary dysplasia
- patent ductus arteriosus.

ROP SCREENING AND PREDICTION

Primary goal of ROP screening – identifying the disease at a stage appropriate for intervention.

Treatment window of opportunity - disease should be identified at a stage where treatment is needed but not beyond where treatment would be effective.

ROP screening is a misnomer because it is the professional eye examination by an Ophthalmologist and must be no false negatives unlike in other disease screening which was conducted by non-physicians like screening of vision and laboratory screening blood tests.

Screening the preterm infants who are at risk of developing ROP at right time helps in early treatment of severe ROP with good visual outcome.

Screening protocol for ROP is given by National Neonatology Forum (NNF) and it includes

- All preterm neonates born < 34 weeks gestation and/or
- All preterm neonates with < 1750 grams BW and
- Babies born 34-36 weeks gestation or 1750-2000 grams BW along with the presence of risk factors for ROP (cardiorespiratory support, Respiratory distress syndrome, prolonged oxygen requirement, fetal haemorrhage, chronic lung disease, sepsis, blood transfusion, apnoea, intraventricular haemorrhage) are to be screened.
- The first ROP screening retinal examination should be done not later than 4 weeks of age in babies born ≥ 28 weeks of GA and early, by 2-3 weeks of age in babies born < 28 weeks of GA or < 1200 grams BW for early identification of AP-ROP.

But, only 8% screened infants require treatment for severe ROP with current screening protocol. This shows that, current screening protocol needs modification.

Formulation of easier and effective screening tool which predicts the development of "severe ROP" helps in identification of high risk babies and reduces unnecessary stressful examinations to no/low risk babies.

Several studies suggest that poor weight gain and low serum IGF-1 in early postnatal period is strongly correlated with development of severe ROP later and also predicts the development of severe ROP.[50,51]

The role of IGF-1 in prediction of ROP was confirmed in several studies. Study by Pérez-Muñuzuri et. al. found that serum IGF-1 at three week post-partum in 74 preterm infant of Spanish population have a 90% sensitivity in prediction of ROP independent of GA at birth.[52]

In study by Pieh et. al, 42 preterm infants were assessed for plasma sE-selectin levels, 2 to 3 weeks after birth and found to be significantly increased in ROP patients suggesting it as a predictor for ROP.[53]

"Follow up examination schedule based on retinal findings:

Zone I:

Immature retinal vascularisation	– 1-2 weeks follow up
Stage 1 or 2	– 1 week or less follow up
Regressing ROP	– 1-2 weeks follow up

Zone II:

Immature retinal vascularisation	– 2-3 weeks follow up
Stage 1	– 2 weeks follow up
Stage 2	– 1-2 weeks follow up
Stage 3	– 1 week or less follow up
Regressing ROP	– 1-2 weeks follow up

Zone III:

Stage 1 or 2	– 2-3 weeks follow up
Regressing ROP	– 1-2 weeks follow up"

“ET-ROP protocol for treatment includes,

Type 1 ROP called new threshold, treatment is peripheral retinal ablation includes

Zone II: stage 2 or 3 with plus disease

Zone I : stage 1, 2, or 3 with plus disease

Zone I : stage 3 without plus disease

Type 2 ROP called low risk prethreshold ROP, wait and watch for progression includes

Zone II: stage 3 without plus disease

Zone I : stage 1 or 2 without plus disease”

AP-ROP requires ablative laser therapy, stage 4 or stage 5 ROP requires vitreo-retinal surgical intervention.

DISCONTINUING SCREENING

Unless eyes have been treated (laser and/or anti-VEGF) for severe form of ROP, treating ophthalmologist can discontinue ROP screening examination if any of the following criteria are met.[38]

Full retinal vascularisation

Zone III retinal vascularisation without previous zone I or zone II ROP

Lack of development of worse or prethreshold ROP by 50 weeks of PMA

Regressing ROP in zone III without abnormal vascular tissue, which is capable of reactivation in zone II or zone III.

Ultimately, decision must be tailored to individual’s disease course.

CLASSIFICATION OF ROP [54,55]

The International Classification for Retinopathy of Prematurity (ICROP) provides standards that promote collaborative clinical investigations and was updated in 2005 to reflect our modern understanding of ROP features.

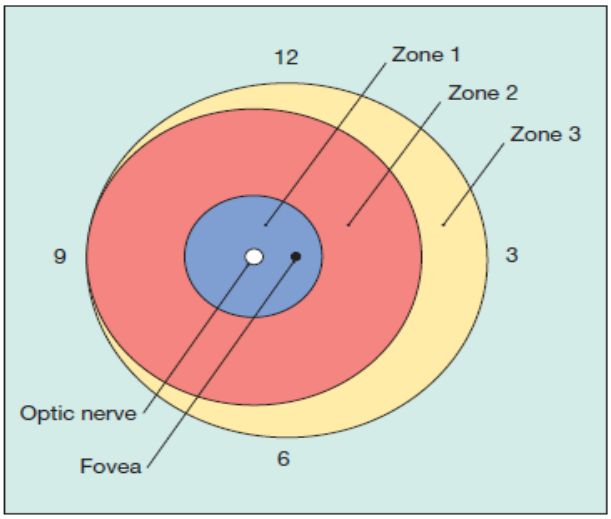
The parameters used in ICROP:

Zone,

Stage (extent of the stage of ROP is no longer used in describing the severity) and

Presence of plus disease.

ZONES OF RETINOPATHY OF PREMATURITY:



Zone I - circle centered on optic disc whose radius is double the distance from the optic disc to the foveal center. It subtends an arc of about 60 degree.

A clinical correlate for estimating the temporal extent of zone I is to place the nasal margin of optic disc in the field of view of a 28D lens, with the limit of zone I being the temporal field of view.

Zone II - circle peripheral to zone I with a radius from optic nerve to nasal ora serrata. Temporal boundary corresponds approximately to the anatomic equator.

Zone III - remaining temporal crescent of retina anterior to zone II, is the last to become vascularised.

STAGES OF RETINOPATHY OF PREMATURITY

Based on

- "Location of retinal involvement
- Extent of involvement by clock hour
- Stage of the disease at the junction of vascular and avascular retina"

Vascular stages i.e stages 1-3, defined by

- appearance noted at the junction of vascular and avascular retina.

Fibrovascular stages i.e stages 4 and 5, defined by presence of

- vitreous traction and fibrovascular membranes
- area of retinal detachment and macular involvement

STAGE 1 – "DEMARCATION LINE"

First visible sign of ROP using ophthalmoscope.

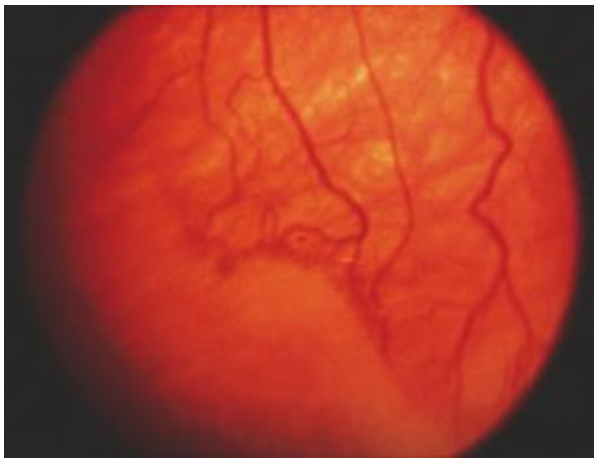
Appearance - flat and white structure between avascular and vascular retina.

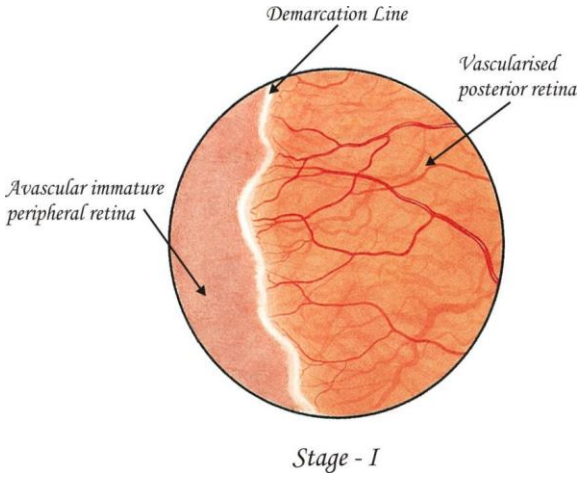
Lies within the retinal plane.

Abnormal arcading of vessels can lead up to the line.

It either progress to ROP stage 2 or involutes to normal vascularisation.

According to Garner,[56] it has two relatively distinct zones morphologically, "vanguard, the anterior zone has spindle-shaped cell mass and these are considered to be progenitors of the differentiated vascular endothelium". Hyperplasia of these makes the demarcation line visible ophthalmoscopically.





Stage - I

STAGE 2– "RIDGE"

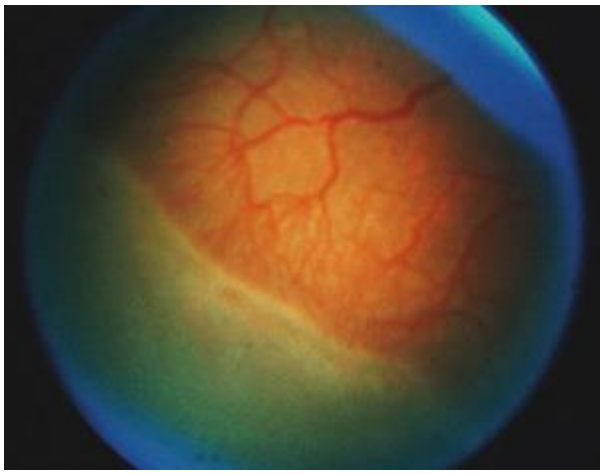
The demarcation line has become a ridge with height and width and extends centripetally within the globe.

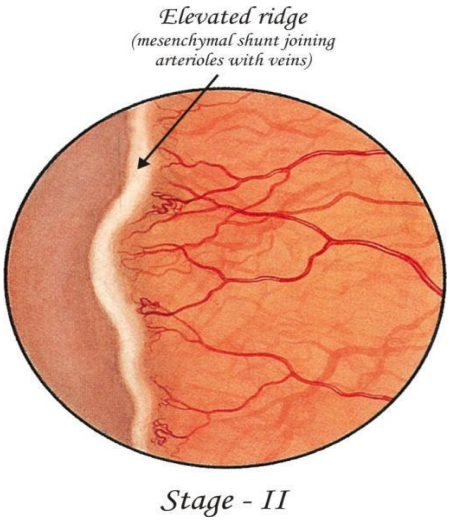
Ridge colour - white or pink

Rarely vessels may leave the retinal surface to enter it.

Posterior to the ridge structure small tufts of new vessels ("popcorn" lesions) may be seen but is not attached with the ridge.

According to Garner,[56] it is due to endothelial cell proliferation "with some evidence of organization into recognizable vascular channels." On fluorescein angiography these channels shows leakage.[57]





Stage - II

STAGE 3 – "RIDGE WITH EXTRARETINAL FIBROVASCULAR PROLIFERATION"

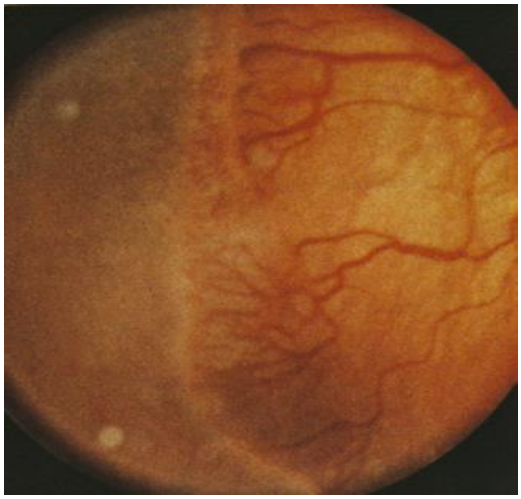
Extraretinal, fibrovascular tissue proliferation occurs from former ridge.

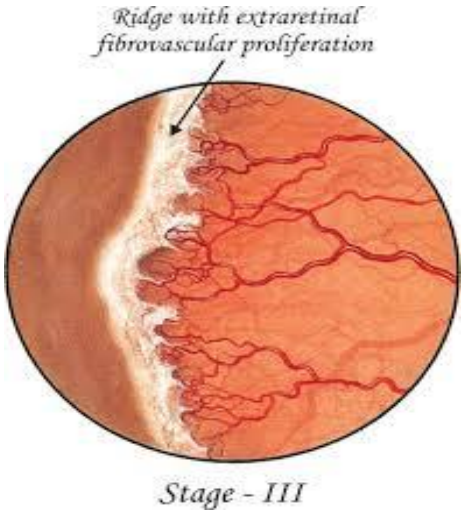
It is localized and is continuous with posterior aspect of the ridge, giving a ragged appearance to it, with increase in proliferation into the vitreous.

Depending on the amount of proliferative tissue it is subdivided into 3 stages- mild, moderate and severe.

According to Foos, appearance of extraretinal vascularisation on histological examination may be placoid, polypoid, or pedunculated.[58]

The most common and important is placoid, because this pattern can progress to retinal detachment.





According to Foos, "extraretinal vessels are derived from proliferating endothelial cells and not from the mesenchymal spindle cells", vitreous changes are synchysis and condensation.[66]

RETINAL DETACHMENT

Most common form observed in acute ROP is tractional retinal detachment. It originates at the ridge, at which point there is a pull of myofibroblast centripetally towards the lens in purse-string configuration.

Peripheral detachment which occurs posterior to the ridge can proceed to total detachment in a week. At this stage peripheral retinal cryoablation appears to reduce by half the incidence of childhood RD.

Exudative retinal detachment occur less commonly in acute ROP. This occurs as result of plasma leakage from abnormal neovascular tufts and leads to sub retinal fluid accumulation.

Sometimes chronic vitreoretinal traction has a role in exudation. Retinal findings are smooth retinal detachment with yellow exudates; small angioma with retinal haemorrhage can be seen. Sometimes intravitreal anti-VEGF can be used in this condition.

Rhegmatogenous retinal detachment occur very rarely**.**

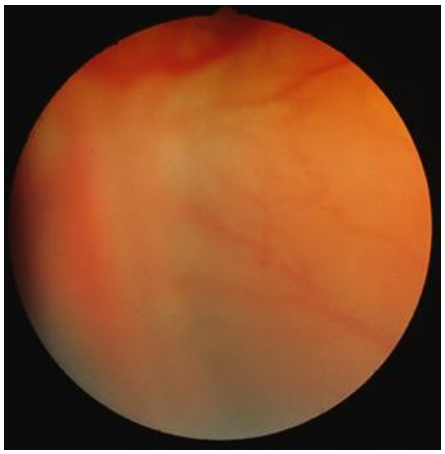
STAGE 4 –PARTIAL RETINAL DETACHMENT[58-60]

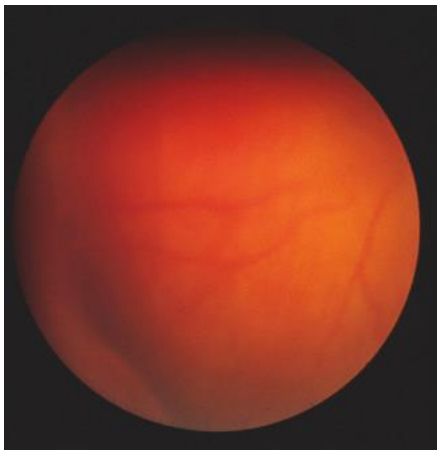
STAGE 4A: "EXTRAFOVEAL RETINAL DETACHMENT"

Concave, traction detachment of the peripheral retina without involving macula and occur at the site of extraretinal fibrovascular proliferation with vitreous traction. It may be segmental or circumferential for 360 degree. In the absence of posterior extension

prognosis is relatively good. Spontaneous reattachment may occur without affecting macular function.

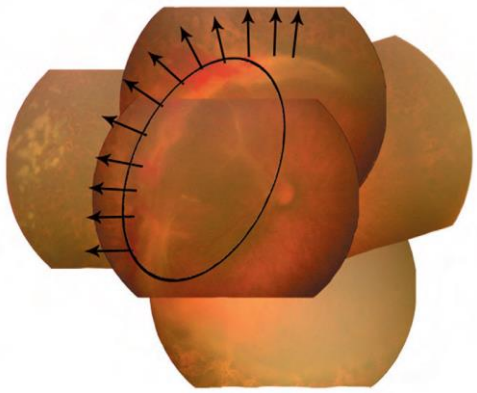
BOTH EXUDATIVE AND TRACTIONAL	EXUDATIVE TYPE





STAGE 4B: "PARTIAL RETINAL DETACHMENT INVOLVING THE FOVEA"

Partial retinal detachment as a result of fibrovascular proliferation involving the macula and visual prognosis is poor because of macular involvement.

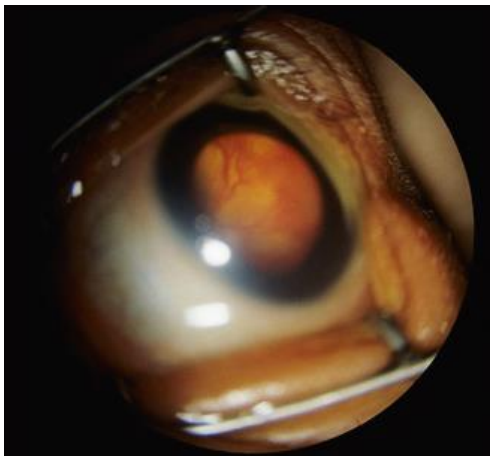
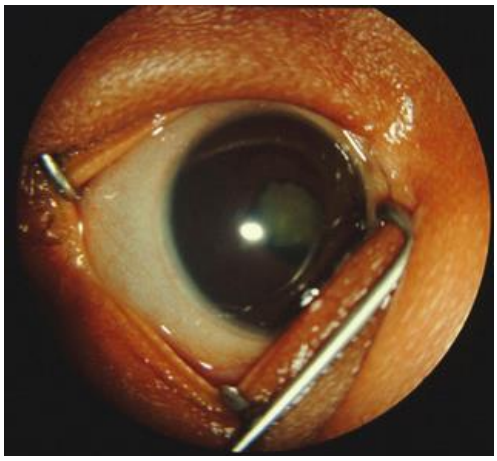


STAGE 5: "TOTAL RETINAL DETACHMENT"

It is usually funnel-shaped and classified as "open" or "closed" anteriorly or posteriorly based on shape of the funnel.

- First common type - concave configuration and is open anteriorly and posteriorly and extends upto disc.
- second type - funnel is narrow anteriorly and posteriorly.
- Third type- funnel is open anteriorly and narrow posteriorly.
- Fourth least type - funnel is narrow anteriorly and open posteriorly.

These configurations are detected by ultrasonography. Sometimes adherence of detached retina to posterior lens capsule may be seen.

OPEN FUNNEL RD	CLOSED FUNNEL RD
	

“PLUS” AND “PRE-PLUS” DISEASE

“Plus disease” - “dilatation and tortuosity of retinal arteries and veins in the posterior pole” and is indicator of poor outcome.[61] It is associated with pupillary rigidity, iris vascular engorgement and vitreous haze. CRYO-ROP trial introduced standard photographs as the minimum abnormality necessary for plus disease diagnosis.[62]

Plus disease is postulated to occur either by shunting of blood through the neovascular ridge or as a response to increased VEGF acting on the blood vessels themselves.

Revised ICROP guidelines defined “preplus disease” – “dilatation and tortuosity of posterior pole vessels that is insufficient to diagnosis as plus disease”.

PLUS DISEASE

PLUS DISEASE

AGGRESSIVE POSTERIOR ROP

Used to describe posterior disease (zone I or posterior zone II)

Characterized by dramatic plus disease that appears out of proportion to extent of retinopathy.

It progresses to retinal detachment without evolution through the classic stages.

It can have circumferential vessels at the junction of vascular and avascular retina, and also flat neovascularisation.

INVOLUTION OF RETINOPATHY OF PREMATURITY

"Involution of ROP"- downgrading of ROP stage and/or growth of retinal vasculature into a more peripheral zone and it begins after 38 weeks of PMA.[64]

RETINAL FINDINGS OF "REGRESSED ROP"

Residual changes of regressed ROP[65,66] is classified as,

- Retinal periphery changes and
- Posterior fundus changes

Peripheral and posterior changes are further classified into vascular and retinal changes.

Peripheral vascular changes are

- Failure to vascularise peripheral retina
- Vascular arcades with circumferential interconnection
- Abnormal, non-dichotomous branching of retinal vessels
- Telangiectatic vessels

Peripheral retinal changes are

- Pigmentary changes
- Lattice-like degeneration and retinal breaks
- Traction or rhegmatogenous RD

Posterior Vascular changes are

- Vascular tortuosity
- Abnormality in the angle of insertion of major temporal arcade
- Blood vessels get straightened in temporal arcade

Posterior Retinal changes are

- Pigmentary changes
- Dragging of retina over disc
- Distortion and ectopia of macula.

OCULAR FINDINGS OF "REGRESSED ROP"

- Myopia,[57]
- Astigmatism, anisometropia ,[68]
- Amblyopia,
- Strabismus, nystagmus,
- Glaucoma.
- Lens changes - cataract,[69]
- Corneal changes - band keratopathy, corneal curvature irregularities and acute hydrops.[55]

CICATRICIAL DISEASE

20% of infants with active ROP develop cicatricial complication from mild to extremely severe form.[65,66] More advanced and more posterior to the proliferative disease at the time of involution develop worse cicatricial sequalae.

Stage 1: Pigmentary changes in peripheral retina and vitreous base haze.

Stage 2: Vitreoretinal fibrosis and straightening of temporal vascular arcades follows dragging of macula and disc.

Stage 3: Severe fibrosis of peripheral retina with contracture and falciform retinal fold.

Stage 4: Incomplete ring of retrolental fibrovascular tissue with total RD called as retrolental fibroplasias occur. Progressive shallowing of anterior chamber is caused by forward movement of iris-lens diaphragm and development of anterior synechiae and

secondary angle closure glaucoma. Lensectomy and anterior vitrectomy can be tried but results are poor.

Cicatricial macular changes classification:[70] "MS – Macular score"

"MS-0 Normal

MS-1 Macular ectopia

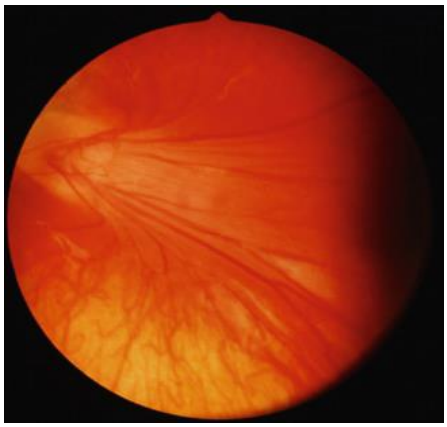
MS-2 Macular fold

MS-3 Macular detachment

MS-4 Total detachment"

MACULAR HETEROTOPIA

MACULAR FOLD



DIFFERENTIAL DIAGNOSIS

1. FAMILIAL EXUDATIVE VITREORETINOPATHY

This condition associated with neovascular disease may be indistinguishable from acute ROP. It resembles changes seen in stage 1 to 3 ROP.

Differentiating feature is no history of prematurity, positive family history, asymmetry in both eyes. Changes in familial exudative retinopathy may be detected anytime from birth to ten years of age.

2. RETINOBLASTOMA

It is also one of the differential diagnosis of stage 5 ROP and differentiation is based on the history of prematurity, asymmetrical presentation. Ultrasonography confirms the diagnosis.

It shows posterior mass lesion with calcification. In contrast, ultrasonography in ROP shows complex pattern of multiple echoes behind the lens or retinal detachment.

3. PERSISTENT HYPERPLASTIC PRIMARY VITREOUS (PHPV)

It is a congenital anomaly that occurs in term infants. Unilateral condition associated with microcornea, greyish white membrane behind the lens which has to be differentiated from ROP. Vessels are seen behind the lens in retinal detachment of ROP. In PHPV, retina is usually attached and stalk extends from optic disc to posterior lens surface.

4. COAT'S DISEASE

It arises from abnormal telangiectatic retinal vessels. Features are retinal edema due to profuse leakage from telangiectatic vessel, yellow-green subretinal material and exudative detachment. Leucocoria is the initial presentation of these cases.

5. NORRIE'S DISEASE

It is X-linked disorder presenting with leucocoria, deafness and mental retardation. Examination at 4-6 weeks of age presenting with leucocoria is confused with ROP. Leucocoria in ROP present in very late stage due to stage 5 ROP.

5. INCONTINENTIA PIGMENTI

Multisystem disorder affecting females. It has dermatological, dental and neurological findings. Ocular features include preretinal neovascularisation, peripheral retinal vascular nonperfusion, vitreous haemorrhage and tractional retinal detachment. Term at birth and characteristic vesicobullous lesion differentiates from ROP.

PREVENTION

Best treatment for ROP will be prevention.

By addressing the strategies to decrease the incidence of premature birth and low birth weight, it is possible to prevent ROP.

Reducing high risk pregnancies, better prenatal care thereby prolonging gestation and promoting the avoidance of illegal drug use helps to reduce the incidence of ROP.

Several studies were conducted and ongoing to address the strategies to prevent the development of "severe ROP".

In the 1990s the "STOP-ROP study"[71], a multicetre trial was conducted with goal of eliminating the hypoxic stimulus for new vessel formation.

In this trial, 694 infants with prethreshold ROP were assigned in a random manner to maintain O_2 saturation levels of 96%-99% in supplemental group versus 89%-94% in conventional group.

Result showed no statistical difference between the two groups (41% versus 48%) in rate of threshold ROP progression.

In the subgroup of infants with prethreshold ROP without plus disease, a post hoc analysis was done and result showed progression to threshold ROP in the supplemental arm was significantly reduced (32% versus 46%).

Of concern is that adverse pulmonary events and increased duration of hospital stay occurred more frequently in the supplement group. Several studies demonstrated the beneficial role of carefully regulating the oxygen saturation levels within specific limits.

Studies from 2003 to 2006 demonstrated significant decrease in prethreshold disease and "severe ROP" after institution of criteria to maintain oxygen saturation between 85%-93%.

However, some studies showed increased mortality even though the severity of ROP was reduced if oxygen saturation target maintained between 85%-89%.

The LIGHT–ROP trial was conducted to test the hypothesis that reduced extrauterine light using light–blocking goggles from birth to 31 weeks of postconceptional age would decrease the ROP incidence but found no clinical or statistical difference between treatment and control groups.[72]

Recent experimental evidence suggested that in late gestation, exposure to greater light may be a factor in hyaloidal regression and retinal vascular development.

Studies conducted to test antioxidants including vitamin E and D-penicillamine showed mixed results.[73]

RET CAM II

Ret cam II was current technique of screening for retinopathy of prematurity[74]. As the number of premature babies is rising, Ret cam becomes easy to screen the premature infants. Ret cam images are clear and reliable.

Portability and the features of Ret cam made it tool for diagnosis and teaching purpose. Ret cam II consists of contact retinal camera which is placed over the cornea with the help of coupling fluid.

Choice of lenses available is 30, 80, 120, 130 degrees and portrait. Wide field image is captured and it is converted into digital, high resolution colour photograph.

TREATMENT

Aim of the ROP treatment is maximal preservation of neurosensory retinal structure and function with minimal complications. Clinical studies found that peripheral diode laser photocoagulation is superior to cryotherapy in treatment of ROP.[75,76]

Current treatment guidelines are based on clinical trials that attempted to define the mildest form of the disease for which the benefit of treatment would outweigh its risk and lead to improved anatomical and visual acuity outcomes.

Cryotherapy was used in the treatment of ROP since 1972. The CRYO–ROP study included 291 infants with “threshold ROP” and they were randomized to either cryotherapy within 72 hours or observation.

"Threshold ROP was defined as 5 contiguous or 8 cumulative clock hours of stage 3 ROP and plus disease in zone I or zone II" and the estimated risk of progression to an unfavourable outcome was 50%.

The 10-year result of the CRYO-ROP study showed that for untreated eyes with zone II threshold disease, 62% had a poor visual outcome. However for zone I threshold ROP, 87% had poor visual outcome.

Because of significant decrease in unfavourable outcomes such as posterior retinal folds, retinal detachment, or development of retrolental tissue in the treatment group (31% treated versus 51% observed), the CRYO-ROP study was terminated early. 254 infants were followed for fifteen-years which demonstrated the long-term benefits of treatment.

There was also a decreased incidence of poor visual acuity in treated eyes. (45% treated versus 64% observed).[77]

Availability of indirect laser photocoagulation was not widely available at the time of the CRYO-ROP study.

However, in the study the favourable outcome were presumed to be due to the ablation effect on the peripheral avascular retina and it was extrapolated to be similar if laser were used.

Some studies demonstrated that laser treated eyes had better structural and functional outcomes compared to cryotherapy treated eyes.

Later a study was conducted to determine whether early treatment of ROP would result in better outcomes.

In ETROP study, eyes at risk of developing "threshold ROP" was defined as "prethreshold ROP" and it was further subdivided into type1 ROP, in which there was ≥15% chance of unfavourable outcome based on eye and infant characteristics from the CRYO-ROP and type 2 ROP, in which <15% chance of unfavourable outcome.

ETROP finding demonstrated that type 1 ROP benefited with peripheral laser ablative treatment to the avascular retina and type 2 ROP observation twice-weekly until the disease either progressed to a higher-risk category or improved.

At the end of 9 months, result showed that in the earlier treatment group unfavourable visual outcomes were reduced to 14.5% when compared to 19.5% in the conventional group (treatment for threshold disease). Both of these results were statistically significant.

Follow up at the end of 6 years showed fewer unfavourable structural outcomes in early treated eyes. Visual acuity outcomes were not statistically significant at 6 years; but, subgroup analysis demonstrated improved visual acuity for eyes with zone I in the early treatment group.[78]

CURRENT GUIDELINES RECOMMENDED INITIATING TREATMENT OF SEVERE ROP WHEN CRITERIA FOR TYPE 1 ROP ARE MET.

If type 1 ROP develops, ablation of avascular retina by laser photocoagulation should be performed within 72 hours based on the ETROP protocol.[78]

From the ora serrata upto the avascular retina but not including the ridge for 360 degree, grey to grey white burns spaced one-half laser burn width.

Systemically, infants are at risk of bradycardia, apnoea and cardiopulmonary arrest during or following treatment and must be followed closely.

Ocular complications are rare but include misplacement of laser burns, post laser inflammation, cataract, vitreous hemorrhage, glaucoma secondary to anterior rotation of the lens-iris diaphragm, and extremely rarely, pthisis bulbi.

Topical steroids and cycloplegics are given for a short time after treatment. Treated eyes are followed within 3-7 days and then weekly or more frequently.

Persistent or recurrent disease is treated with further laser and vitreoretinal surgery is considered for progressive stage 4 ROP.

The "BEAT-ROP" study ("Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity") tested bevacizumab (anti-VEGF antibody), given intravitreally at 0.625 mg in 0.025 ml in 150 infants.[79]

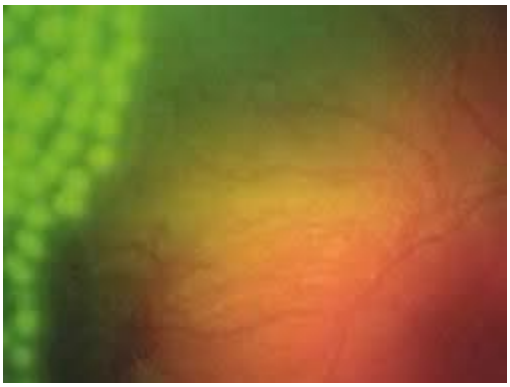
It benefited the babies with zone I stage 3+ ROP.

This study was too small to assess the effects of bevacizumab on development of brain and other tissues, and did not address drug dosage and is also not FDA approved drug for ROP treatment. Bevacizumab is used only for zone I stage 3+ROP after getting detailed informed consent.

Following treatment, examinations are done weekly until complete vascularisation of the retina. Follow up exams must be done for a longer period than after conventional laser ablation treatment, because recurrent stage 3 ROP can occur at later time than after conventional laser treatment. Assure follow up after bevacizumab treatment particularly after discharge or transfer from a neonatal unit.[80,81]

LASER PHOTOCOAGULATION

Ablation of ischemic avascular retina stops the release of angiogenic factors and this forms the basic principle of management.



Advantage

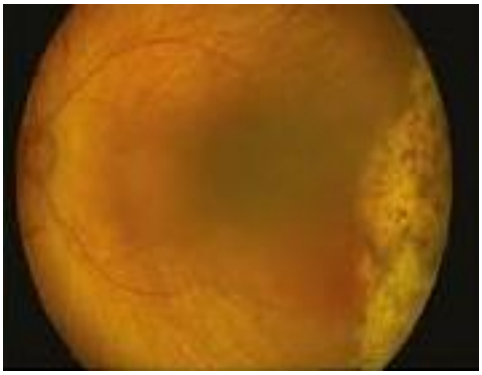
- Treatment of more posteriorly located disease, where cryoprobe is not accessible.
- Good structural and functional outcome
- No need for general anaesthesia

Procedure

- Written informed consent from parents or legal guardian should be obtained
- Nature of disease, disease progression, complication and long term sequelae to be explained to the parents
- Retreatment, surgical intervention and long term follow up also to be explained
- Feeds to be deferred at least half an hour prior to the treatment.
- Neonatologists and anaesthetist should be there during the procedure
- Pupillary dilatation to be adequate
- In case of incubator dependant infants, procedure to be done in incubator with sloping walls
- Portable infra-red diode laser, frequency doubled Nd: YAG laser or an argon laser can be used
- Laser indirect ophthalmoscope delivers the laser. Diode laser is used worldwide for treatment as it penetrates the eyes with tunica vasculosa lentis and vitreous haemorrhage
- Paediatric lid speculum applied, with wire vectis or scleral depressor indentation is done.
- Using 20 or 28 D aspheric lens visualisation of the retina is done
- Power of diode laser varies from 300 to 400mw and the duration of laser is 300 to 400ms.
- Laser settings should be kept minimum to produce light grey burns

- Ablation of entire avascular retina from ridge to ora in near confluent burn pattern to be done
- Less than half burn width should be as getting close to edge of the ridge.
- Confluent treatment has less progression compared to dense laser treatment.
- Laser spots are delivered in areas enclosed by flat neovascular loops as in case of aggressive ROP
- Mechanical pupillary dilatation can be done in case of poor dilatation of pupil due to tunica vasculosa lentis.
- Carboxymethyl cellulose topically provides the clear view of cornea during the procedure.
- Antibiotic -steroid eye drops to be instilled for 1week to control inflammation
- Some premature infants develop apnoea during laser treatment and they need resuscitation and ventilator support.

BEFORE LASER TREATMENT	AFTER LASER TREATMENT



- Conjunctival chemosis and subconjunctival haemorrhage may develop in case of excessive scleral indentation.
- Preretinal and vitreous haemorrhage rarely occur
- Intense photocoagulation sometime cause anterior segment ischemia and necrosis

Follow up

Follow up is usually done at 1week. Response is assessed by

- Extent of plus disease
- Presence of skip areas
- Status of ridge and fibrovascular proliferation
- Vitreous organization
- Presence or absence of vitreous haemorrhage
- Tunica vasculosa lentis

Additional laser, in case of significant plus disease with skip areas are still present. Plus disease without skip areas, to be followed weekly interval. Follow up should be done till the regression of ROP occurs.

If there is no fibrovascular proliferation baby should be followed upto 6months of age.

In case of significant fibrovascular proliferation close follow up at weekly interval for tractional retinal detachment should be done.

SURGICAL MANAGEMENT-RETINAL DETACHMENT[82-84]

According to ETROP study sixteen percent of patients with type 1 ROP had retinal detachment in at least 1 eye.

Of these, 38% of patients had bilateral retinal detachment. Half of the retinal detachments were in stage 4 and half were in stage 5. Classification of retinal detachment - effusive (serous), tractional (fibrovascular), and rhegmatogenous.

Serous retinal detachment is believed to be caused by leakage from vascular structures into the retina and subretinal space and this type presents with convex shape, often posterior to the ridge, with extension towards the macula and lens.

Tractional retinal detachment demonstrates fibrovascular tissue causing peaked retinal folds.

Serous stage 4 ROP often resolves spontaneously, and observation or surgical intervention can be made appropriately on an individual basis. Retinal detachment can occur within 12 weeks of laser treatment in 14% of eyes received laser treatment.

Treatment of advancing stage 4 ROP is lens-sparing vitrectomy to release fibrovascular traction and without creating any holes allow the retina to settle back spontaneously and is optimal to prevent progression to stage 5 ROP and preserve macular structure.

Additionally, sclera buckling procedure can be done for treatment of advancing stage 4 ROP.

For stage 5 ROP treatment options include vitrectomy with or without sclera buckle and only scleral buckle.

In aphakia, visual rehabilitation is difficult and every attempt should be made to preserve the lens during vitrectomy procedure; however, even when a lens sparing vitrectomy is performed, in 5%-15% of cases cataract may occur.

Poor outcomes for all interventions are associated with the presence of plus disease, persistent neovascularisation, and vitreous haze. Scleral buckling is associated with high myopia, anisometropia and amblyopia.

OTHERS THERAPIES

Major angiogenic factors responsible for ROP pathogenesis is VEGF. VEGF levels in vitreous of babies with vasoproliferative ROP were assessed and found to be significantly elevated.[85]

Studies in animal models showed suppression of neovascularisation with VEGF.[86,87] In ROP several reports exist about the off-label use of bevacizumab as anti-angiogenic therapy which was either used alone or in conjunction with laser treatment.

Lee et. al. studied 15 cases treated for ROP stage 3 with both intravitreal bevacizumab and laser ablation and noted regression of plus disease with rapid development of the peripheral retinal vasculature and also noted that no significant difference in systemic and ocular complications compared to laser therapy alone.[88]

In ROP treatment, considerable concerns remain as to the safety of anti-VEGF, especially regarding to “the time of injection, correct dosage and potential local complications such as lens damage, adverse effects on retinal neurosensory development,

infection and unknown systemic effects in children with already persistent subnormal growth, impaired cortical function"

Therefore, randomized control trials are needed to establish the safety and efficacy of bevacizumab in ROP treatment before reliable statements can be made.

Numerous research works in angiogenesis suggest a several new methods to interfere in the progression of ROP includes

- Targeting the IGF-1 pathway[89,90] and
- Supplementation of omega-3 polyunsaturated fatty acids in diet.

Lack of IGF-1 prevents the development of normal retinal vasculature despite the presence of VEGF.

After birth if IGF-I level is adequate, development of retinal vessels occur normally without development of ROP in premature babies.

Persistently low IGF-I retards the retinal vessel growth, maturing avascular retina becomes increasingly hypoxic and leads to VEGF accumulation in vitreous.

These factors suggest that in premature infants IGF-I predict whether the baby will develop ROP or not.[91]

Early reinstitution of IGF-I in preterm babies may prevent the development of ROP. Study conducted in Sweden showed that combination of "IGF-I and IGF-binding protein 3 complex" in preterm babies was safe.

Therefore, IGF-1 supplementation in ROP phase I would hypothetically normalize the retinal vascular development thereby preventing abnormal vascular proliferation in ROP phase II.

A clinical trial is underway "to investigate the possibility of preventing ROP in preterm babies by restoring IGF-1 to the in utero levels".[92]

Recently in ROP animal model studies showed that pathologic neovascularisation is protected by dietary supplementation of omega-3 PUFAs.

At present to treat severe cases of neovascular ROP, laser photocoagulation is the only well established treatment.

VISUAL REHABILITATION

Infants who developed ROP are more likely to develop high myopia, strabismus, amblyopia, macular heterotropia and glaucoma.

Infants who are aphakic or have a sclera buckle in place require rehabilitation with special treatment for high refractive error.

Babies with more severe form of ROP may not develop macular vision; however, spectacles can be given to improve the vision and provides protection against ocular trauma.

In an early intervention program, all visually impaired babies should be enrolled and that teaches them to fully utilize their impaired vision and other senses.

Infants with ROP may have other comorbidities that contribute to poor vision which include intraventricular hemorrhage, cerebral visual impairment, and hydrocephalus.

MEDICOLEGAL CONSIDERATIONS

Screening of premature infants for ROP and treatment is an essential aspect in the practice of ophthalmology. There are three aspects in ROP care which places the premature infant and the entire healthcare team at risk.

First, premature babies who are at risk of ROP development typically have multiple medical consultants responsible for their care. Appropriate steps should be taken to ensure that treating ophthalmologists are kept aware of status and location of the babies they follow so that screening examinations are not missed.

Second, parents of premature infants often feel overhelmed and effort should be needed to ensure compliance with screening, treatment and follow up at the appropriate intervals.

Third, the treatment window for ROP is very short and treatment may require transfer of a critical patient. The entire team of neonatologists, ophthalmologists, and nurses become targets of ligitation when protocols for ROP care break down. Ophthalmologists who is doing ROP examination and treatment can optimize care for the babies and minimize their exposure to lawsuits by educating parents and documentation in the medical record.

AIMS AND OBJECTIVES

To analyse the postnatal weight gain in babies with “no ROP”, “mild ROP” and in babies with “severe ROP”.

To determine the role of weight gain in early postnatal period in predicting the development of severe ROP requiring treatment in preterm babies, in our hospital.

MATERIALS AND METHODS

STUDY DESIGN:

Prospective observational study

STUDY PERIOD:

This study was conducted from March 2016 to August 2016 for a period 6 months.

STUDY CENTRE:

Department of Ophthalmology, Government Rajaji Hospital, Madurai.

Institute of Paediatrics, Government Rajaji Hospital, Madurai.

SAMPLE SIZE:

Total sample size was 100 babies fulfilling the eligibility criteria.

ETHICAL APPROVAL:

Institutional ethical clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai.

INFORMED CONSENT:

Informed written consent obtained from parent or guardian of all babies before enrollment.

SELECTION OF STUDY SUBJECTS:

100 babies fulfilling the eligibility criteria for ROP screening were selected from those attending ROP screening clinic in Eye department OPD and as inpatient in Neonatal Intensive Care Unit of Government Rajaji Hospital, Madurai.

INCLUSION CRITERIA:

- Babies born less than 34 weeks gestation and or
- Babies born with birth weight less than 1750 grams.

EXCLUSION CRITERIA:

- Babies with non-physiological weight gain includes
- ✓ hydrocephalus,
- ✓ congestive cardiac failure and
- ✓ hydrops.
- Babies with obvious congenital anomalies.
- Babies expired before the completion of ROP screening.

METHODOLOGY:

Parameters recorded were Infant's birth weight, gestational age at birth, postconceptional age and other risk factors such as long term exposure to oxygen, mechanical ventilation, surfactant use, Respiratory Distress Syndrome, septicaemia, multiple blood transfusions, multiple births, apnoeic episodes and intraventricular haemorrhage.

Gestational age calculated according to last menstrual period or first trimester abdomen sonogram.

The screening examination for ROP followed in our study was based on guidelines proposed by NNF (National Neonatology Forum).

The first retinal examination was performed at 4 to 5 weeks of age.

Ocular examinations were carried out by binocular indirect ophthalmoscope with +20 D lens and findings were recorded in the ROP screening case sheet.

Revised ICROP classification was used for categorization of ROP. Follow up examinations were based on the retinal findings and continued until complete vascularisation or regressing ROP was noted or until treated based on the ETROP guidelines.

The main clinical outcome observed was occurrence of severe ROP requiring treatment.

In our study “mild ROP” was defined as ROP that does not meet criteria for treatment based on CRYO-ROP study and ETROP study guidelines and, “severe ROP” was defined as either Type 1 ROP based on ETROP study findings, threshold ROP, AP-ROP, stage 4 or stage 5 ROP that needs treatment.

Babies were divided into two groups.

Group 1: Infants with no ROP and mild ROP.

Group 2: Infants with severe ROP.

WEIGHT MEASUREMENT:

- Infants weighed unclothed before feed on calibrated electronic weighing machine with a digital read out.
- Infant’s weight recorded weekly till 4^{th} week and at 6^{th} week of post natal age, and relative weight gain calculated for the same.
- Relative weight gain calculated by body weight minus birth weight, divided by birth weight and chronological age, (g/kg/day).

PROCEDURE:

- Procedure explained to the parent/guardian.
- The baby fed 1hour before examination.
- Incubator dependant babies were screened within incubator itself.
- Hands washed with 2% of chlorhexidine.

- Both eyes were dilated with combination of tropicamide 0.8% and phenylephrine 5% diluted in tear substitutes in 50:50 ratio, and used two to three times about 10-15 minutes apart prior to examination.
- Excess drops wiped off to avoid systemic absorption of drugs through cheek skin.
- Baby placed in examining couch.
- Drop of topical anaesthetic, 4%lignocaine was instilled into both eyes.
- Paediatric eye speculum applied.
- Retina examined using binocular indirect ophthalmoscope with + 20D lens and retinal periphery using scleral indentation.

- First examination of anterior segment was done to look for the presence of tunica vasculosa lentis, pupillary dilatation and lens/media clarity.
- Followed by posterior pole examination to look for the presence of “plus disease” and sequential examinations of all clock hours of peripheral retina.

STATISTICAL ANALYSIS

The data were analysed with SPSS statistical software package (Version 16.0 SPSS Inc., Chicago, USA).

The relative weight gain was calculated for second week, fourth week and sixth week of postnatal age and compared between "no ROP/mild ROP" group and "severe ROP" group using unpaired student 't' test, P value of <0.05 will be considered as statistically significant.

RESULTS

The study was conducted in department of Ophthalmology and at Institute of Paediatrics in Government Rajaji Hospital, Madurai to analyse poor postnatal weight gain as a predictor for "severe ROP" requiring treatment. Totally 100 babies were recruited for the study after satisfying the inclusion and exclusion criteria. After obtaining informed consent from parents/guardians of babies, they were divided into two groups.

Group 1: Infants with no ROP and mild ROP.

Group 2: Infants with severe ROP.

All the babies were followed until complete vascularisation of retina or regressing ROP or until treatment.

SEX DISTRIBUTION

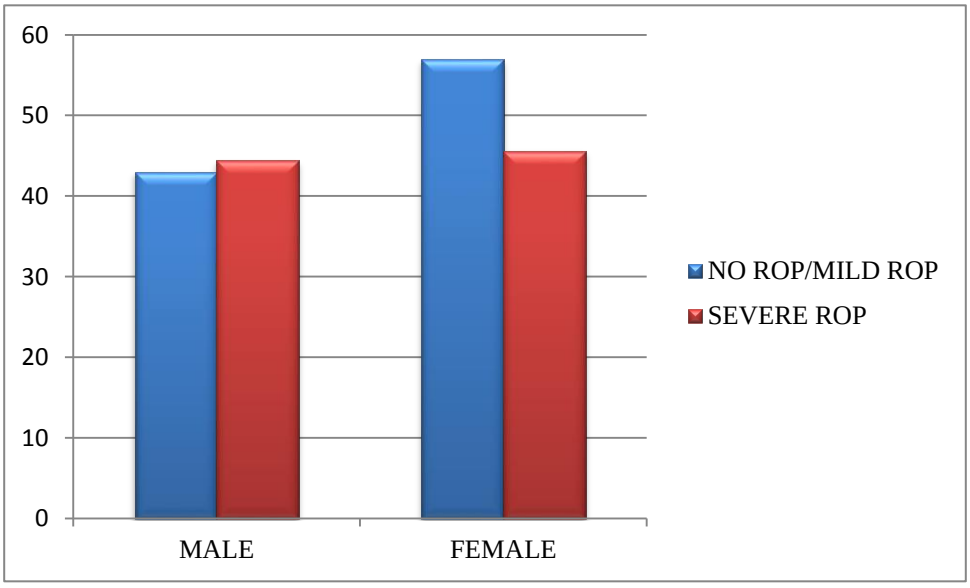
Among 100 babies analysed, 43 were males and 57 were females,

Group 1 had 39 males and 52 females while Group 2 had 4 males and 5 females.

TABLE 1

	MALE	FEMALE
NO ROP/MILD ROP	39	52
SEVERE ROP	4	5

FIGURE 1

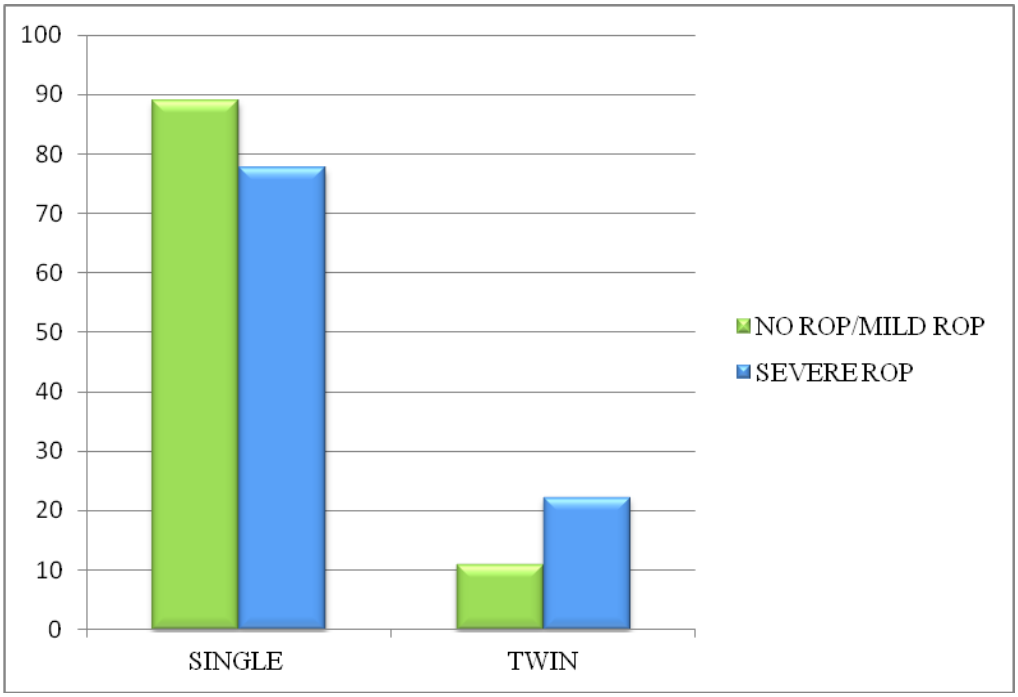


Among 100 babies, 88 were single gestation and 12 were twin gestation, Group 1 had 81 single gestation and 10 twin gestation babies and group 2 had 7 single gestation and 2 twin gestation babies.

TABLE 2:

	SINGLE	TWIN
NO ROP/MILD ROP	81	10
SEVERE ROP	7	2

FIGURE 2



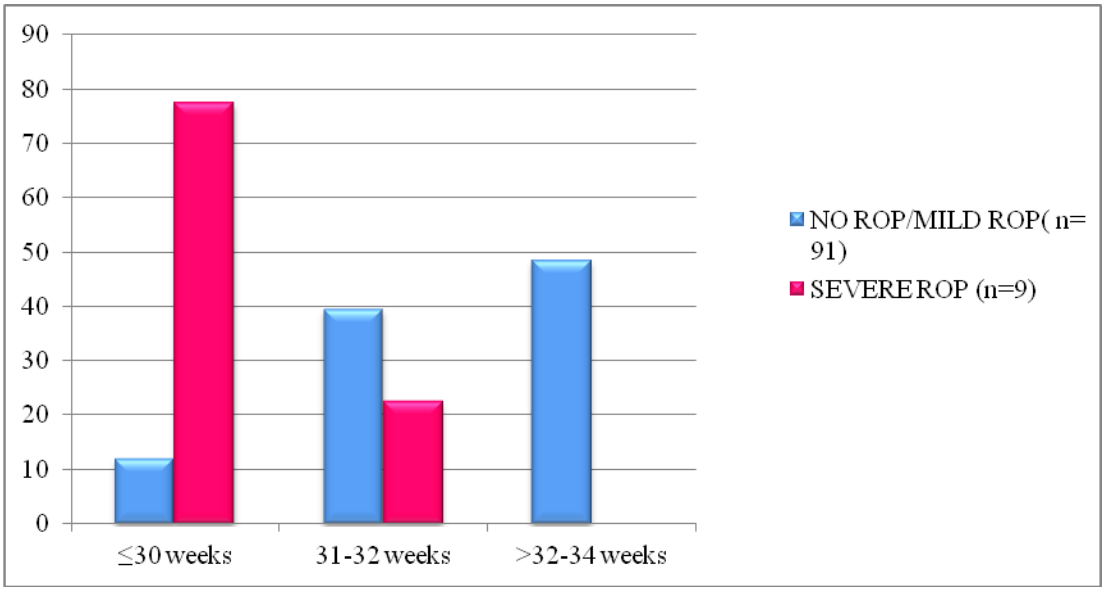
GESTATIONAL AGE DISTRIBUTION

In group 1, mean gestational age at birth was 32.24±1.43 weeks ranged from 28-34 weeks. In group 2, mean gestational age at birth was 29.9±1.04 weeks ranged from 28-32 weeks. Two groups were compared using unpaired student 't' test and found to be significant with P-value of <0.01.

TABLE 3

GESTATIONAL AGE AT BIRTH	≤30 WEEKS	31-32 WEEKS	>32 WEEKS
NO ROP/MILD ROP	11	36	44
SEVERE ROP	7	2	0

FIGURE 3



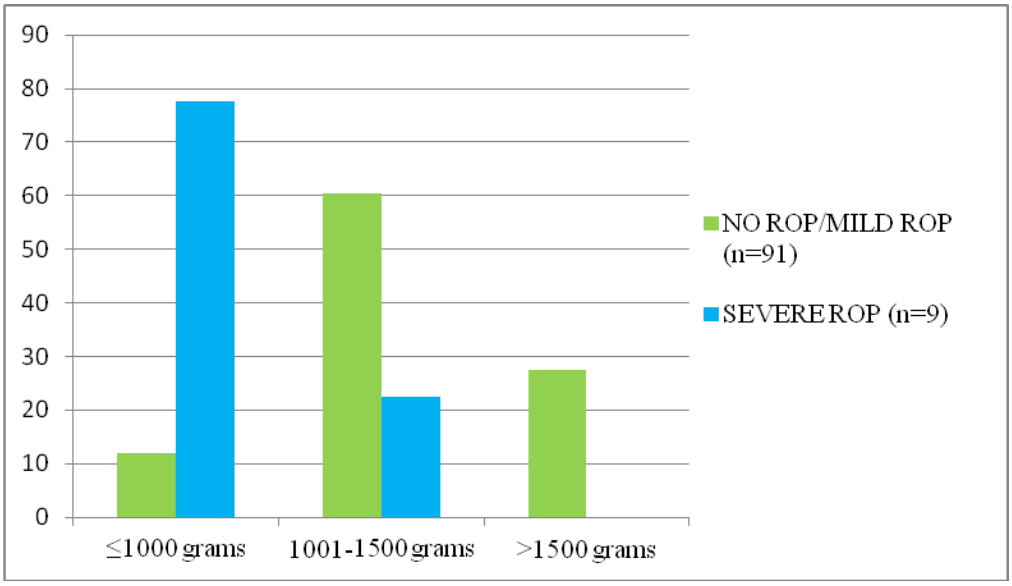
BIRTH WEIGHT DISTRIBUTION

In group 1, mean birth weight was 1396.20±248.23 grams ranged from 1000-1750 grams. In group 2, mean birth weight was 1164.44±140.99 grams ranged from 930-1300 grams. Two groups were compared using unpaired student 't' test and found to be significant with P-value of <0.01.

TABLE 4

BIRTH WEIGHT	≤1000 GRAMS	1001-1500 GRAMS	>1500 GRAMS
NO ROP/MILD ROP	11	55	25
SEVERE ROP	2	7	0

FIGURE 4



INCIDENCE OF ROP

Among 100 babies studied in our hospital,

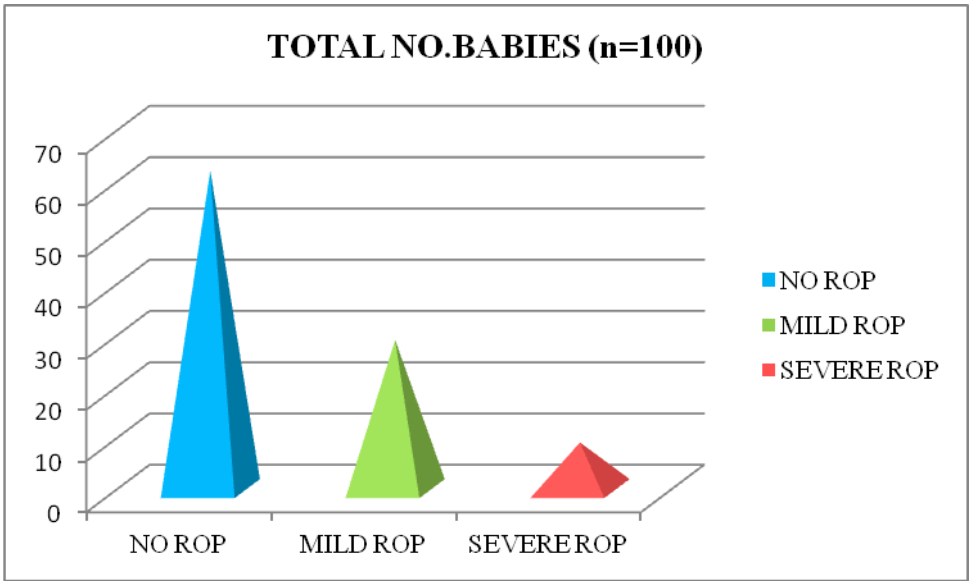
Incidence of ROP was 38% (38/100 babies had any stage of ROP).

Incidence of severe ROP was 9% (9/100)

TABLE 5

	TOTAL NO.BABIES (n=100)
NO ROP	62
MILD ROP	29
SEVERE ROP	9

FIGURE 5

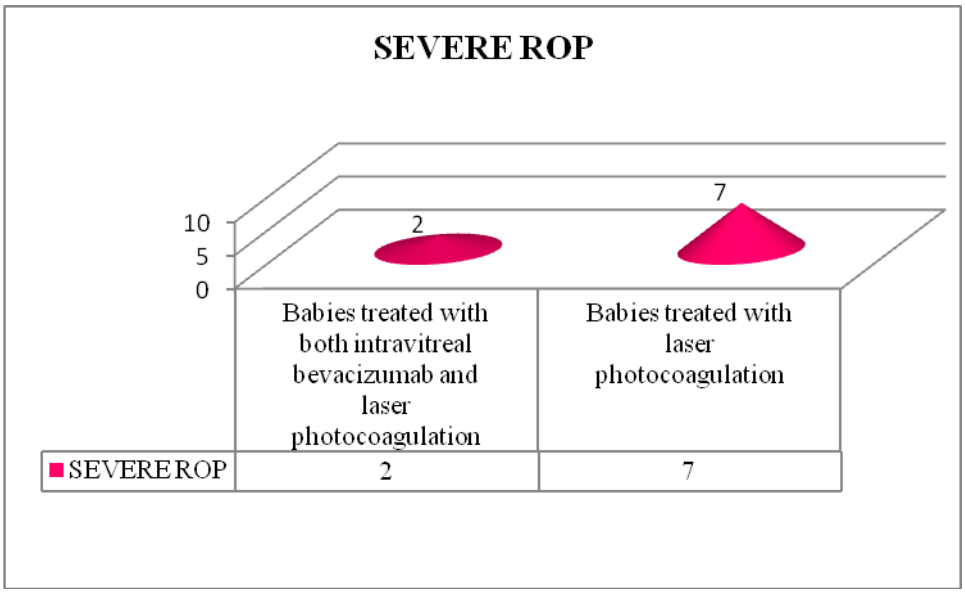


In 9 cases of severe ROP,

2 were treated with intravitreal bevacizumab and laser photocoagulation,

7 were treated with only laser photocoagulation.

FIGURE 6



RELATIVE WEIGHT GAIN CALCULATION:

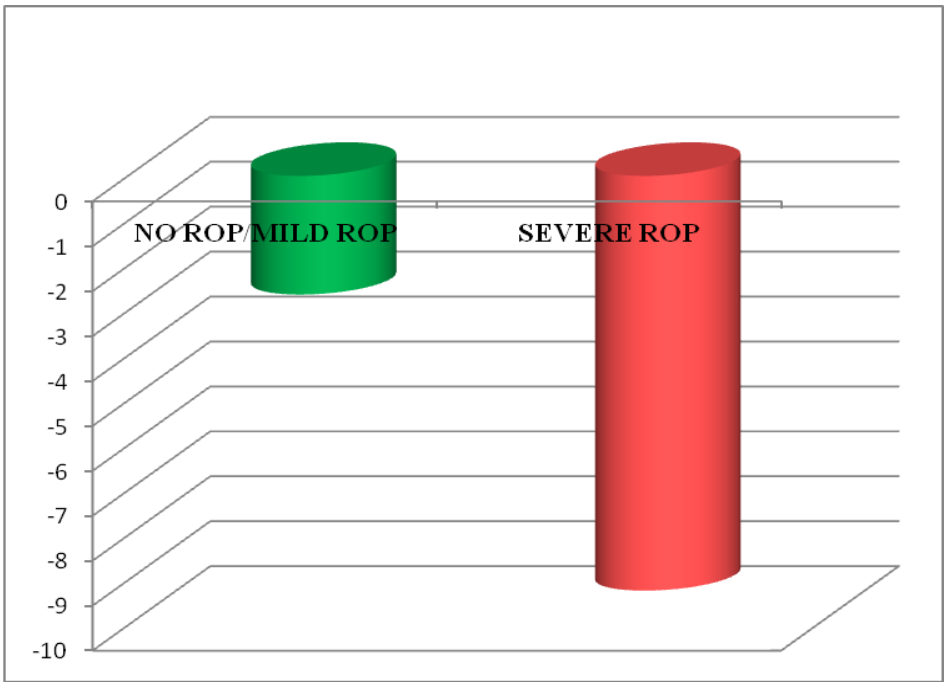
12 babies for whom extremes of relative weight gain observed were excluded in statistical analysis for obtaining precise results and all were in Group 1.

Relative weight gain (g/kg/day) at second week of postnatal life was calculated as mean±SD

Group 1: -2.55±3.55

Group 2: -9.23±3.92

FIGURE 7

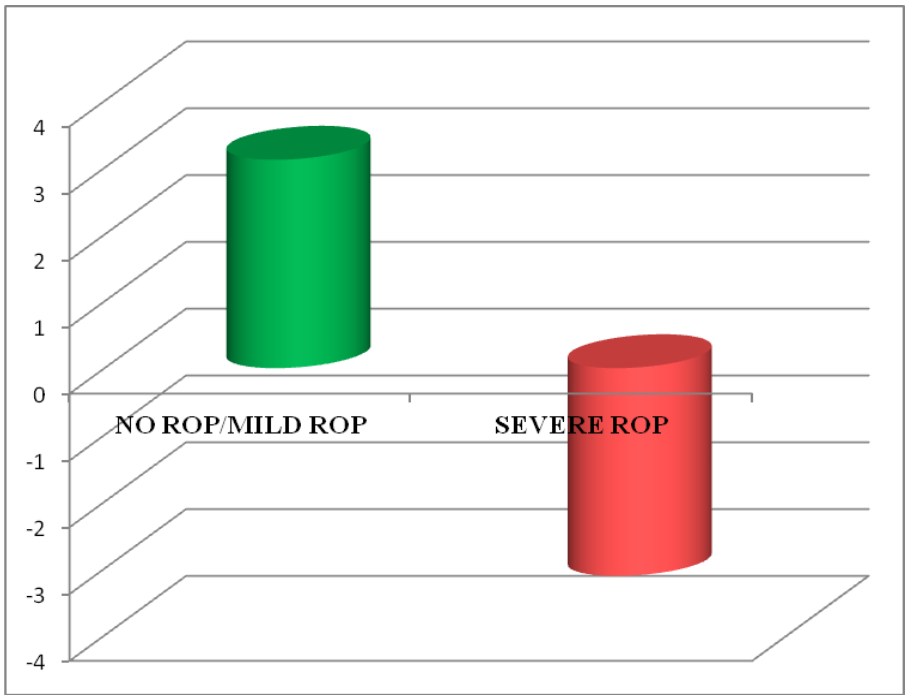


Relative weight gain (g/kg/day) at fourth week of postnatal life was calculated as mean±SD

Group 1: 3.12±3.71

Group 2: -3.11±0.90

FIGURE 8

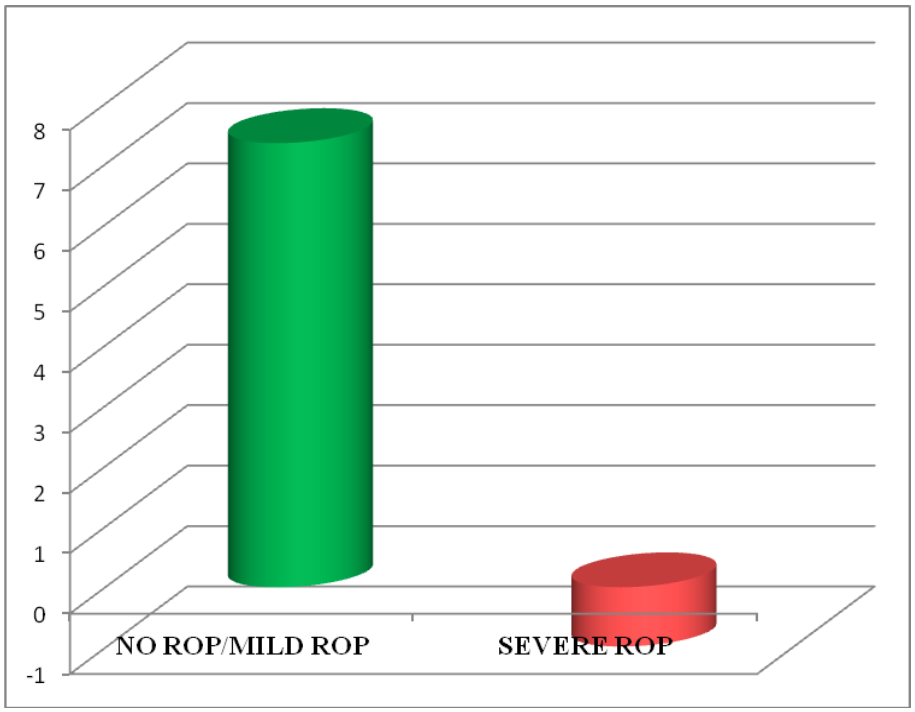


Relative weight gain (g/kg/day) at sixth week of postnatal life was calculated as mean±SD

Group 1: 7.35±4.14

Group 2: -0.98±0.87

FIGURE 9

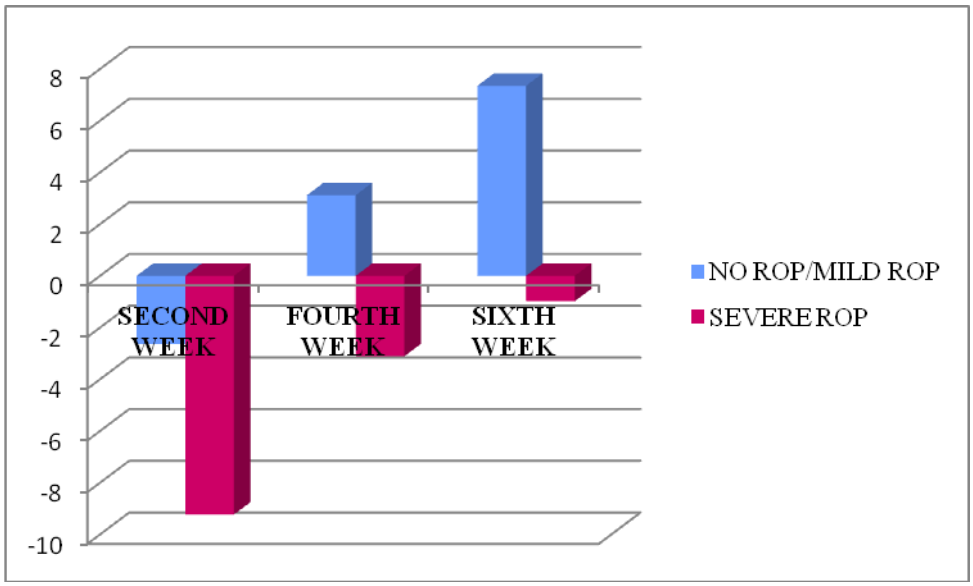


COMPARSION OF RELATIVE WEIGHT GAIN BETWEEN TWO GROUPS:

Relative weight gain between two groups were compared using unpaired student 't' test at second, fourth and sixth week of postnatal life and all found to be significant with P-value of <0.0001.

TABLE 6

RELATIVE WEIGHT GAIN (g/kg/day)	NO ROP/MILD ROP	SEVERE ROP	P-VALUE
SECOND WEEK	-2.55±3.55	-9.23±3.92	<0.0001
FOURTH WEEK	3.12±3.71	-3.11±0.90	<0.0001
SIXTH WEEK	7.35±4.14	-0.98±0.87	<0.0001

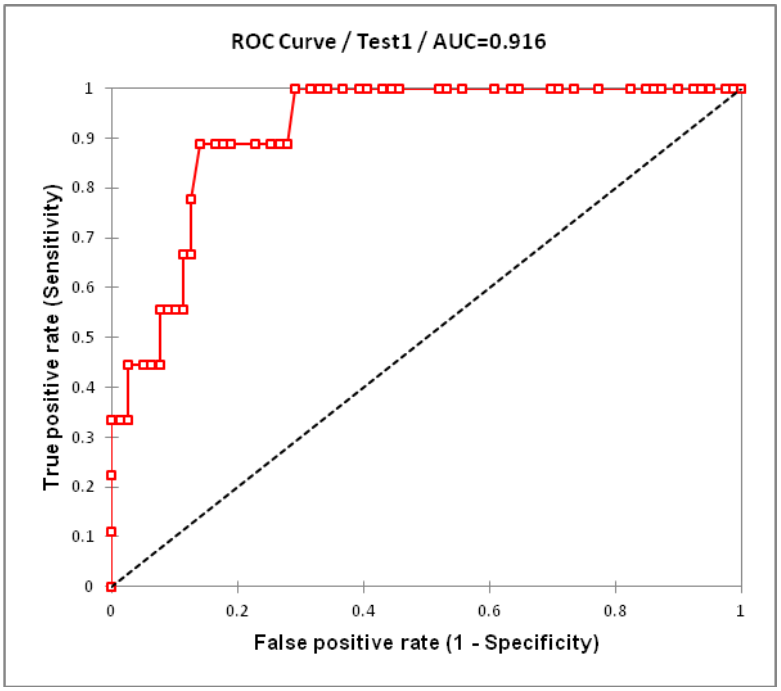


For detection of severe ROP, Receiver Operating Curve (ROC) analysis showed,

Cutoff of –6.2g/kg/day of relative weight gain calculated at second week of life (area under the curve 0.916; 95% confidence interval on the difference between the AUC and 0.5, 0.288-0.543) with

Sensitivity of 88.9% and

Specificity of 86.1%

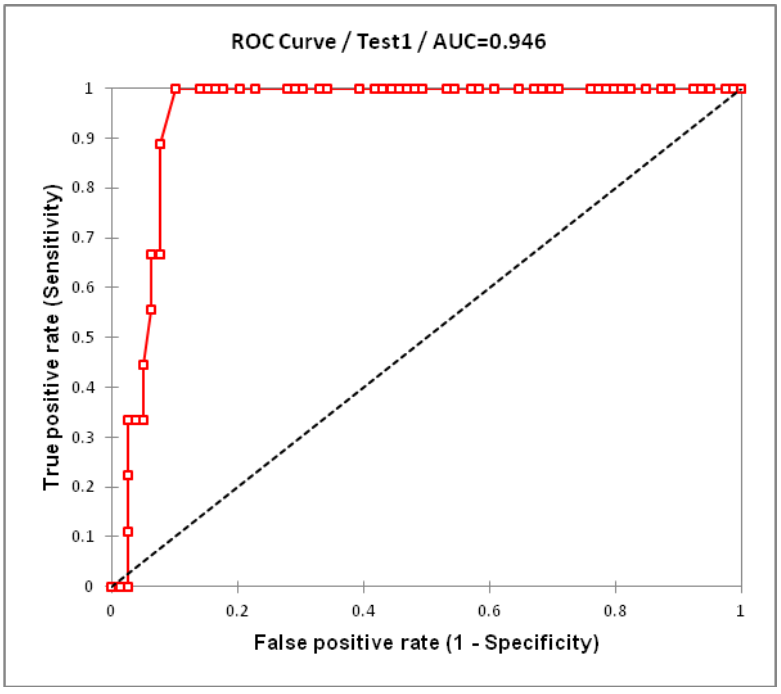


For detection of severe ROP, ROC analysis showed,

Cut off of –1.5g/kg/day of relative weight gain calculated at fourth week of life (area under the curve 0.946; 95% confidence interval on the difference between the AUC and 0.5, 0.342-0.550) with

Sensitivity of 100% and

Specificity of 89.9%

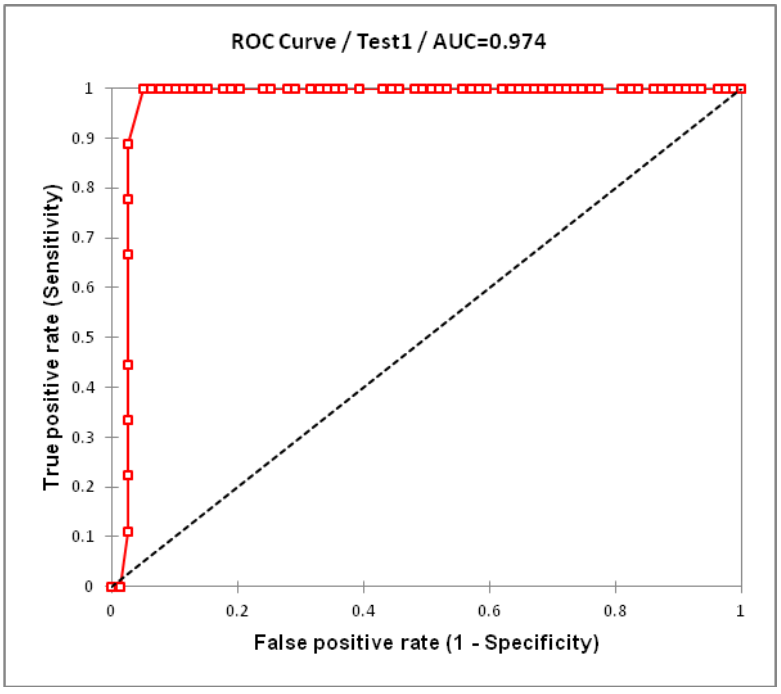


For detection of severe ROP, ROC analysis showed,

Cut off of 1.1/kg/day of relative weight gain calculated at sixth week of life (area under the curve 0.974; 95% confidence interval on the difference between the AUC and 0.5, 0.400-0.548) with

Sensitivity of 100% and

Specificity of 94.9%



SUMMARY OF RESULTS

Among 100 babies in this study, 62 had no ROP, 29 had mild ROP and 9 had severe ROP. Incidence of ROP was 38% and severe ROP was 9%.

The mean GA in group 1 and group 2 were 32.24±1.43 weeks and 29.9±1.04 weeks respectively.

The mean BW in group 1 and group 2 were 1396.20±248.23 grams and 1164.44±140.99 grams respectively. Statistical analysis showed babies with severe ROP had significantly lower BW and GA at birth.

Out of 9 babies with severe ROP, 2 were treated with both intravitreal bevacizumab and laser photocoagulation and 7 were treated with only laser photocoagulation.

Relative weight gain at second, fourth and sixth week of postnatal life were calculated and compared statistically between two groups and it was low in babies with severe ROP with significant P-value of <0.0001.

For detection of severe ROP, ROC analysis identified cutoff value of -6.2g/kg/day of relative weight gain calculated at second week with sensitivity of 88.9% and specificity of 86.1%, -1.5g/kg/day of relative weight gain calculated at fourth week with sensitivity of 100% and specificity of 89.9% and 1.1g/kg/day of relative weight gain calculated at sixth week with sensitivity of 100% and specificity of 94.9%.

DISCUSSION

ROP is caused by abnormal retinal vascular development in postnatal period. Identifying postnatal factors which have a predictive value in development and severity of ROP will be helpful for ROP screening and prevention.

Clinical and animal studies showed that "low serum levels of IGF-1" and "poor postnatal weight gain" are associated with development of "severe form of ROP".[92,93]

Foundation for ROP screening is timely detection and treatment of severe ROP to get better visual outcome.

Weekly measurements of weight in early postnatal period helps in detection of babies at risk for developing severe ROP weeks before may have significant positive effect on care of these babies and predicting severe ROP in babies requiring deferment or rescheduling of ocular examination.

Allagaert et al study showed poor absolute weight gain (g/day) but not relative weight gain in first 6 weeks of life was associated with threshold disease.[94]

Fortes Filho et al study showed low weight gain proportion at 6 weeks of life is an independent risk factor for development of ROP requiring treatment.[95]

These studies were different from our present study in that they used absolute weight gain or weight gain proportion in their studies. However, this have limitations in reflecting the true weight gain, because these premature babies were all born with

different BWs, and smaller babies are expected to have lower weight gain compared to larger babies. Therefore, the more appropriate definition is relative weight gain.

This study calculated relative weight gain at second, fourth and sixth weeks of life and found that "poor relative weight gain at the second, fourth and sixth week of life was capable of predicting the development of severe ROP requiring treatment".

This is supported by study by Wallace et al and it showed that GA and poor relative weight gain in first 6 weeks of postnatal life were independent risk factors for development of ≥stage 3 ROP.[96]

Aydemir et al also used a similar method and they found relative weight gain in 4th week of life was independently lower in babies with severe form of ROP.[97]

An online surveillance system was developed in Sweden based on BW measurements and serum IGF-1 levels weekly in the neonates. Weight IGF-1 Neonatal ROP (WINROP) algorithm was designed to detect the slow rise in IGF-1 levels or weight gain and was compared with values of infants those who have no ROP or only stage 1 ROP. It has 100% sensitivity in detecting babies who will need treatment for ROP.

Later it was modified that only serial weight measurements part of WINROP algorithm, excluding IGF-1 measurement was used, that can also predict severe ROP requiring treatment with 100% sensitivity. This algorithm was validated in Sweden and USA in a different cohort of infants.[98,99]

In 2015 July, American Academy of Ophthalmology published evolving concepts in diagnosis and management of ROP, included poor postnatal weight gain as independent risk factor for developing ROP.

IGF-1 is essential for the normal growth and development of many tissues including brain, retina and blood vessels. Preterm babies have lower serum IGF-1 level after birth due to poor endogenous production and loss of maternal source of IGF.[100]

Sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis, all act via common pathway that reduces IGF-1 level and are associated with development of ROP.

Serum IGF-1 concentration is strongly associated with postnatal weight gain and development of ROP in preterm babies. Postnatal weight gain is used as a surrogate measure for serum IGF-1 level.[101]

This explains the association of relative weight gain at the early postnatal period and development of severe ROP.

This new approach helps to reduce the number of babies requiring stressful eye examination for ROP and precisely targeting babies at risk of developing severe ROP.

This method helps to take more regulated follow up measures for babies with high risk to ensure visit compliance, decreasing the unfavourable outcome from missed ROP appointments, cost effective and readily available.

Early postnatal nutrition is important for postnatal weight gain. Human milk increases infants IGF-1 level and omega 3 fatty acid level that protect against ROP.

New pharmacological treatments to improve physiologic retinal vascularisation e.g omega 3 polyunsaturated fatty acid supplementation, IGF-1 supplementation, erythropoietin supplementation have shown good results in animal studies, but more work is needed before considered for use in preterm infants.

Many randomized clinical trials found the essential nutrient, inositol, to reduce the severity of ROP. Currently, a multicentre randomized clinical trial is underway.

CONCLUSION

The results of this study showed that “poor postnatal weight gain” in early postnatal period is a predictor for development of “severe ROP” requiring treatment with laser photocoagulation and/ or anti-VEGF in our hospital.

It helps in the prediction of the ROP much earlier in infants with poor postnatal course who are at the risk of developing severe ROP with possibility of new preventive treatment and avoids unnecessary stressful examination in preterm infants who are not at the risk of developing severe ROP.

Thus, ophthalmologists and neonatologists should take special care and give more attention to the babies with poor postnatal weight gain to predict the disease much earlier before it is diagnosed by regular ocular examination that helps in early intervention and prevention of sight threatening complications.

ANNEXURES

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PROFORMA

PROFORMA

Name of the Baby	:	Date of screening	:
Gender	:	Address	:
Name of the Parent	:	OP / IP Number	:
Postnatal age	:	Birth place	:
Single/multiple births	:	Postnatal weight measurements	
DOB		First week	:
Birth weight	:	Second week	:
LMP: EDD	:	Third week	:
Gestational age at Birth	:	Fourth week	:
Postconceptional age	:	Sixth week	
Delivery mode	:		
Gestational code	:		
Maternal factors	:		
Fetal risk factors	:		
Systemic examination	:		

OCULAR EXAMINATION:

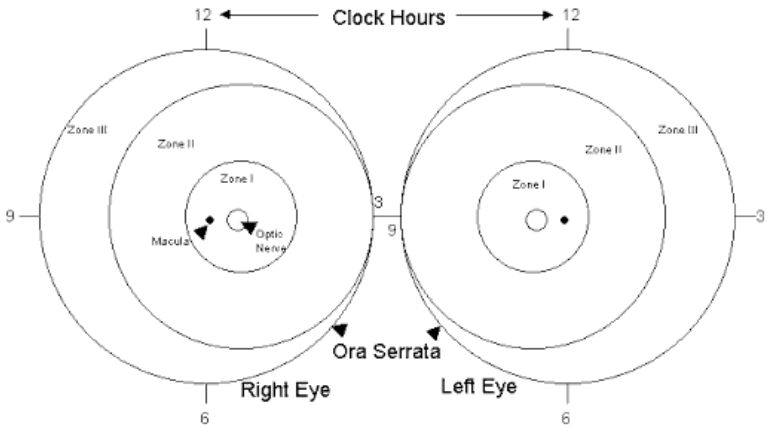
- **ANTERIOR SEGMENT**

OD		OS
	Lids	
	Conjunctiva	
	Cornea	
	Anterior chamber	
	Iris	
	Pupil	
	Lens	
	White reflex	

- **POSTERIOR SEGMENT**

OD		OS
	Media	
	Disc	
	Retinal vessels	
	ROP-Zone, Stage	
	Clock hours involved	
	Fovea	
	Plus disease	

Fundus diagram:



Treatment advice:

Follow-up advice:

Follow up details: No.of visit/Date

MASTER CHART

MASTER CHART														
S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
1	B/O VIJAYALAKSHMI	F	NVD	SINGLE	33	1300	GEATATIONAL HYPERTENSION	O2HOOD-13DAYS, SEPSIS, TRANSFUSION-PLT4, FFP1, PC1	-3.4	-1.4	0.8	2.5	4.9	NO ROP
2	B/O DIVYA	M	LSCS	SINGLE	33	1550	HYPOTHYROID	SEPSIS	-9.7	-4.6	-1.5	1.2	3.6	NO ROP
3	B/O KALEESHWARI	M	NVD	SINGLE	33	1250	PIH	BIRTH ASPHYXIA, HIE, SEPSIS	-6.1	-2.4	0.7	3.7	6.2	NO ROP
4	B/O SATHYA	M	LSCS	TWIN	29	1000	-	BIRTH ASPHYXIA, DIAPHRAMATIC HERNIA, SEPSIS	2.2	6.5	4.8	3.1	5.2	NO ROP
5	B/O NAGAMMAL	F	NVD	SINGLE	33	1750	-	BIRTH ASPHYXIA	-5.6	-2.4	0	9.2	15.5	NO ROP
6	B/O SUNDARI RAJA	M	NVD	SINGLE	34	1600	PIH, ANAEMIA	MILD RDS, TRANSFUSION-PLT3	-3.4	0	1.6	3.6	7.2	NO ROP
7	B/O JOTHILAKSHMI	F	NVD	SINGLE	33	1700	-	O2 HOOD-1DAY	-11.7	-5.4	1.2	2.2	8.7	NO ROP
8	B/O BAKIYA	M	NVD	SINGLE	32	1750	-	RDS, O2HOOD-4 DAYS	-12.5	-8.1	4.6	7.4	10.5	NO ROP
9	B/O PUTHU VASANTHAM	F	LSCS	TWIN	34	1550	-	RDS, O2HOOD-2DAYS	-13.6	-7.4	5.8	9.1	15.6	NO ROP
10	B/O SUDHA	M	LSCS	SINGLE	32	1150	-	O2HOOD-3DAYS, TRANSFUSION-PLT4,FFP5	-10.6	-6.2	-4.6	-1.5	3.5	NO ROP
11	B/O NALLAMAL	F	NVD	SINGLE	33	1700	-	BIRTH ASPHYXIA, CPAP-2 DAYS, O2HOOD-4DAYS	-10.2	-4.3	0	10.3	15.5	NO ROP
12	B/O ANBUSUDHA	M	LSCS	SINGLE	34	1700	-	RD, O2HOOD-2DAYS, NEONATAL JAUNDICE	-5.6	6.8	10.4	15	18.2	NO ROP
13	B/O INDIRA	F	NVD	SINGLE	32	1340	HYPOTHYROID,BOH	RDS, CPAP-2DAYS, O2-7 DAYS,HIE,SEPSIS, TRANSFUSION – PLT3,WB1	-6.2	-4.4	-3.7	-1.5	2.8	NO ROP
14	B/O ROOPA	M	LSCS	SINGLE	33	1750	-	BIRTH ASPHYXIA, CPAP-3DAYS, O2HOOD-4DAYS	-13.4	-7.7	3.4	10.4	22.6	NO ROP
15	B/O MARISELVI	M	NVD	SINGLE	31	1500	PIH	O2HOOD-1DAY	-18.4	-11.2	-6.3	-3.6	3.3	NO ROP
16	B/O NAGALAKSHMI	F	NVD	SINGLE	30	1000		BIRTTH ASPHYXIA, RDS, SEPSIS	-5.8	-1.4	1.2	3.6	8.2	NO ROP
17	B/O VANATHI	F	LSCS	SINGLE	34	1100	PIH	O2HOOD-2DAYS	-5.2	1.8	6.1	10.4	13.5	NO ROP
18	B/O PANDISELVI	M	NVD	SINGLE	32	1200	PIH	BIRTH ASPHYXIA, CPAP-2DAYS, O2HOOD-2DAYS, SEPSIS, TRANSFUSION-PLT2	-6.2	0	1.4	3.4	7.3	NO ROP

S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
19	B/O RAMALAKSHMI	M	LSCS	SINGLE	31	1000	PIH, ANAEMIA	RDS, CPAP-2DAYS, O2HOOD-2DAYS	-6.2	-3.2	0	8.4	17.5	NO ROP
20	B/O KALA	F	LSCS	SINGLE	32	1500	ANAEMIA	O2HOOD-3DAYS, SEPSIS	-11.6	-6.6	-0.7	17.6	23.6	NO ROP
21	B/O BOOPATHY	F	LSCS	SINGLE	33	1500	ANAEMIA	RDS, SURFACTANT, CPAP-12DAYS, O2HOOD-5DAYS	-2.6	2.1	6.3	10.7	13.9	NO ROP
22	B/O DIVYABARATHI	M	NVD	SINGLE	32	1500	ANAEMIA	RDS, O2HOOD-4DAYS	-6.2	-2.3	0	2.3	8.3	NO ROP
23	B/O AMIRTHAPRIYA	M	NVD	TWIN 2	32	1500	-	O2HOOD-1DAY, SEPSIS, CHOROID PLEXUS CYST	-14.5	-7.2	-4.2	-2.4	3.4	NO ROP
24	B/O AMIRTHAPRIYA	M	NVD	TWIN 1	32	1200	-	02HOOD-1DAY, STAPHYLOCOCCUS AUREUS SEPSIS	-5.4	-1.8	1.3	4.5	13.8	NO ROP
25	B/O KAVIARASI	F	NVD	SINGLE	32	1500	PIH	O2HOOD-1DAY, SEPSIS	-7.4	-2.4	1.4	5.4	12.6	NO ROP
26	B/O TAMIL SELVI	F	LSCS	SINGLE	34	1375	PIH	RDS, CPAP-4DAYS, O2 HOOD-3DAYS, SEPSIS, TRANSFUSION-FFP1,WB1	-4.4	-1.8	3.6	8.4	14.6	NO ROP
27	B/O KAVITHA	F	NVD	SINGLE	30	1000	GDM	RDS, O2HOOD-3DAYS, TRANSFUSION-PLT1	-6.4	-3.6	1.7	4.1	17.8	NO ROP
28	B/O KAVITHA	F	NVD	SINGLE	31	1500	PIH	RDS, CPAP-2DAYS, O2HOOD-5DAYS, TRANSFUSION-FFP3,PLT1, IVH, ASD	-8.2	-4.2	-2.3	5.4	7.1	NO ROP
29	B/O THILAGAVATHY	F	NVD	SINGLE	32	1000	PIH, ANAEMIA	RDS, O2HOOD-2DAYS	-9.4	-3.5	2.4	4.2	5.3	NO ROP
30	B/OMEENAKSHI	F	LSCS	SINGLE	28	1200	-	O2-2DAYS	-15.4	-9.2	-3.9	1.3	5.4	NO ROP
31	B/O KARTHIGA	M	NVD	TWIN	33	1400	HYPOTHYROID	RDS, O2HOOD-4DAYS	-6.2	-2.6	1.4	3.4	8.5	NO ROP
32	B/O SOORYA	F	NVD	TWIN	32	1350	-	ROUTINE RESUSCITATION, SEPSIS	-5.1	-1.9	1.6	3.4	5.8	NO ROP
33	B/O PAUNTHAI	M	NVD	SINGLE	33	1300	-	RDS, O2HOOD-2DAYS, Rh-INCOMPATIBILITY, PFO	-4.8	-1.6	2.2	4.1	7.5	NO ROP
34	B/O RAJESWARI PITCHAI	M	LSCS	SINGLE	33	1650	PIH	RDS, CPAP-5DAYS, O2HOOD-8DAYS, SEPSIS, TRANSFUSION-FFP1,PLT4, ASD	-8.4	-2.8	0	2.3	5.6	NO ROP
35	B/O PREMA	M	LSCS	SINGLE	32	1750	-	MILD RDS, SEPSIS	-4.2	5.4	11.4	15.6	18.3	NO ROP
36	B/O MANIKAVALLI	M	NVD	SINGLE	31	1250	-	O2HOOD-3DAYS, ASD, SEPSIS	-4.2	-1.4	0	1.9	4.4	NO ROP
37	B/O SUNDHARI	M	NVD	SINGLE	34	1600	PIH	O2 HOOD-1DAY	-4.4	-1.8	2.2	6.4	12.6	NOROP

S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
38	B/O BEGAM	F	NVD	SINGLE	32	1000	PIH	RDS ,O2 HOOD-4DAYS, CPAP -2DAYS, SEPSIS	-5.4	-1.2	1.1	3.8	13.4	NO ROP
39	B/O DHANALAKSHMI	M	NVD	SINGLE	33	1250	PIH	RDS, O2HOOD-3DAYS	-7.4	-1.8	0	2.9	6.6	NO ROP
40	B/O KARPAGAVALLI	M	NVD	SINGLE	31	1500	PIH	RDS, O2HOOD-4DAYS	-4.8	-1.4	1.2	2.7	4.9	NO ROP
41	B/O SARANYA	F	LSCS	SINGLE	34	1200	PIH	TRANSFUSION-FFP4,PLT3, SEPSIS	-9.7	-5.6	-2.5	1.8	4.6	NO ROP
42	B/O SARITHA	F	LSCS	SINGLE	33	1200	PIH	O2HOOD-1DAY, ASD	-6.2	-3.6	5.6	10.4	15.8	NO ROP
43	B/O SELVI	F	LSCS	SINGLE	34	1500	PIH	ROUTINE RESUSCITATION	-8.4	-1.2	5.4	9.4	14.8	NO ROP
44	B/O SUBALAKSHMI	F	NVD	SINGLE	33	1700	PIH, ANAEMIA	O2HOOD-1DAY	-5.2	1.7	4.2	6.1	10.2	NO ROP
45	B/O MUTHULAKSHMI	F	NVD	SINGLE	32	1500	PIH	RDS, O2-4DAYS, CPAP-1DAY, TRANSFUSION-2PLT	-12.7	-5.6	-1.5	1.4	3.6	NO ROP
46	B/O KANAGA	M	LSCS	SINGLE	32	1600	PIH	ROUTINE RESUSCITATION	-5.6	2.7	7.6	10.4	16.2	NO ROP
47	B/O PALANIYAMMAL	M	LSCS	SINGLE	33	1650	PIH	SEPSIS	-4.1	1.5	3.6	6.3	10.8	NO ROP
48	B/O THANYA	F	NVD	SINGLE	34	1500	PIH	ROUTINE RESUSCITATION	-11.7	-6.6	-1.5	1.4	5.6	NO ROP
49	B/O THILAGA	F	LSCS	SINGLE	34	1400	PIH	O2HOOD-1DAY	-4.3	0	2.4	4.8	8.2	NO ROP
50	B/O ALAGAMMAL PARAMASIVAM	F	NVD	TWIN	32	1350	-	RDS, O2HOOD-4DAYS	-6.4	-1.1	-3.2	2.1	4.8	NO ROP
51	B/O ALAGUPILLAI	F	NVD	TWIN	32	1200	ANAEMIA	RDS, SURFACTANT, CPAP-2DAYS, O2HOOD-5DAYS	-1.1	2.7	4.6	5.1	10.8	NO ROP
52	B/O MEENAKSHI MURUGAN	M	NVD	SINGLE	31	1250	-	RDS, SURFACTANT, O2HOOD-6DAYS, CPAP-4DAYS, SEPSIS	-11.5	-6.2	-2.6	2.4	6.3	NO ROP
53	B/O ANNALAKSHMI	F	NVD	SINGLE	33	1730	-	ROUTINE RESUSCITATION	-5.2	-1.1	2.6	3.2	8.8	NO ROP
54	B/O SUBHA	F	NVD	SINGLE	33	1750	-	RDS,O2HOOD-2DAYS	-9.7	-5.2	-1.5	1.2	5.1	NO ROP
55	B/O BHUVANESHWARI	F	LSCS	TWIN	34	1500	-	SEPSIS	-12.8	-6.4	0	3.8	10.6	NO ROP
56	B/O DEIVAM	F	LSCS	SINGLE	32	1500	-	O2HOOD-3DAYS	-12.2	-7.1	-2.7	0.8	3.8	NO ROP
57	B/O DHIVYA SENTHIL	M	NVD	SINGLE	33	1400	-	TRNSFUSION-PC2,FFP4	-9.1	-5.4	-1.4	2.2	7.4	NO ROP
58	B/O KALPATHRANI	M	LSCS	SINGLE	32	1650	-	O2HOOD-3DAYS	-7.4	-3.3	3.2	8.4	14.6	NO ROP
59	B/O KANIMOZHI	F	NVD	SINGLE	33	1720	ANAEMIA	ROUTINE RESUSCITATION	-4.2	1.4	4.2	7.4	13.1	NO ROP

S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
60	B/O PRIYA KUMARAVEL	F	LSCS	SINGLE	32	1250	-	RDS,O2HOOD-4DAYS, CPAP-1DAY, TRANSFUSION-PLT4,FFP6	-8.4	-3.6	-1.5	2.2	5.6	NO ROP
61	B/O KOKILAVANI	M	LSCS	SINGLE	33	1670	-	O2HOOD-1DAY	-6.2	-2.4	2.1	4.2	8.6	NO ROP
62	B/O MUTHUMARI	M	NVD	SINGLE	33	1300	HYPPOTHYROID	MILD RDS, TRANSFUSION-PL4,FFP3	-7.1	-4.3	-1.6	5.6	11.3	NO ROP
63	B/O KALEESHWARI MUTHU	M	NVD	SINGLE	29	1000	PIH	BIRTH ASPHYXIA, CPAP-2 DAYS, O2HOOD-6 DAYS, HIE	-4.5	2.14	4.5	6.6	9.5	MILD ROP
64	B/O SHANMUGA SUNDARI	F	NVD	SINGLE	31	1500	ANAEMIA	RDS, CPAP-6 DAYS, O2 HOOD-2DAYS, SEPSIS	-9.5	-3.3	-0.7	2.2	2.3	MILD ROP
65	B/O SUDHA	F	LSCS	SINGLE	33	1300	PIH	RDS, CPAP -6 DAYS, O2 HOOD-3DAYS, SEPSIS	-7.3	-3.5	3.2	5.4	6.2	MILD ROP
66	B/O SANGEETHA	F	NVD	SINGLE	28	1250	PIH	BIRTH ASPHYXIA, CPAP-4 DAYS, O2 HOOD-2 DAYS, SEPSIS	-6.1	-3	-2.7	-2.1	0.6	MILD ROP
67	B/O SHOBANADEVI	F	NVD	SINGLE	32	1250	HYPOTHYROID	RDS, CPAP-2 DAYS, O2-4 DAYS	-2.3	-1.1	0	5.7	5.4	MILD ROP
68	B/O RAJESWARI	F	NVD	SINGLE	34	1750	-	CPAP-4 DAYS, SIMV-5DAYS, O2 HOOD-5DAYS, SEPSIS	-2.3	-1.3	0	1.3	6.1	MILD ROP
69	B/O MUTHALEESWARI	M	NVD	SINGLE	31	1500	ANAEMIA	ROUTINE RESUSCITATION	-3.4	-1.9	-0.4	0.5	7.3	MILD ROP
70	B/O SUBITHA PRINCY	F	LSCS	SINGLE	32	1600	GDM	SEPSIS	-5.7	-2.7	-1.3	0	4.5	MILD ROP
71	B/O REKHA	M	NVD	TWIN	31	1250	-	MILD RDS, CPAP-2DAYS, O2HOOD-3DAYS	-9.4	-5.7	-2.1	1.6	4.4	MILD ROP
72	B/O NIVEDHA	M	LSCS	SINGLE	34	1250	-	RDS, O2HOOD-2DAYS, TRANSFUSION-PL3, FFP3	-2.4	2.9	3.6	4.1	5	MILD ROP
73	B/O LAKSHMI	F	NVD	SINGLE	28	1100	ANAEMIA	RDS, SURFACTANT GIVEN, CPAP-3DAYS, O2HOOD-5DAYS, APNOEA, TRANSFUSION-PL3	-13	-8.4	-4.3	-3.3	1.1	MILD ROP
74	B/O MARIYAJAYANTHI	F	NVD	SINGLE	32	1250	-	RDS, SURFACTANT GIVEN, CPAP-1DAY, O2HOOD-2DAYS	-6.2	-2.8	-1.9	1.4	4.3	MILD ROP
75	B/O SAKTHIDEVI	F	NVD	SINGLE	32	1300	ANAEMIA, PIH	RDS, O2HOOD-3DAYS	-11.7	-7.6	-6.1	-8.5	-2.1	MILD ROP

S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
76	B/O CHANDRA	F	NVD	SINGLE	33	1250	PIH, GDM	RDS, CPAP-8DAYS, SIMV-6DAYS, SURFACTANT GIVEN, SEPSIS, PDA	-11.2	-6.1	-5.9	-7	-1.9	MILD ROP
77	B/O MUKILA	M	LSCS	SINGLE	34	1500	PIH	RDS, SURFACTANT GIVEN, SIMV-4DAYS, CPAP-5DAYS, O2HOOD-3DAYS	-2.3	1.8	2.8	4.1	10.7	MILD ROP
78	B/O PANDEESHWARI	F	LSCS	SINGLE	35	1250	PIH, HYPOTHYROID	BIRTH ASPHYXIA, CPAP-2DAYS, O2HOOD-6DAYS, SEPSIS	-2.1	2.9	7.5	8.9	15.8	MILD ROP
79	B/O KAVIYA	M	NVD	SINGLE	30	1500	-	RDS, SURFACTANT GIVEN, CPAP-3DAYS, O2HOOD-3DAYS,HIE	-9.8	-4.3	1.4	1.9	4.6	MILD ROP
80	B/O ARUMUGADEVI	M	NVD	SINGLE	32	1750	-	RDS, SURFACTANT GIVEN, CPAP-8 DAYS, O2HOOD-8 DAYS, SEPSIS	-6.3	-1.5	1.9	3.5	8	MILD ROP
81	B/O NATHIYA MALAISAMY	F	NVD	SINGLE	30	1250	PIH, ANAEMIA	RD, O2HOOD-3DAYS	-6.4	-2.4	0.1	1.4	4.4	MILD ROP
82	B/O USHA	F	NVD	SINGLE	34	1700	-	RDS, O2HOOD-3DAYS, SEPSIS, PDA	-2.5	2.1	4.8	6.6	9.4	MILD ROP
83	B/O VIMALA	F	LSCS	SINGLE	33	1000	-	O2HOOD-3DAYS	-6.3	1.4	6.1	9.4	14.5	MILD ROP
84	B/O RAJESWARI	M	LSCS	SINGLE	33	1750	-	O2HOOD-2DAYS, SEPSIS	-6.3	-1.6	2.9	5.4	10.8	MILD ROP
85	B/O ANITHA PRABHAKARAN	F	NVD	SINGLE	30	1000	-	RDS, O2HOOD-4DAYS,SEPSIS, HIE, TRANSFUSION-FFP3,PLT3	-11	-7.3	-5.8	-1.5	2.7	MILD ROP
86	B/O MALAISELVI	F	LSCS	SINGLE	34	1100	PIH	O2 -1DAY, SEPSIS	-8.33	-5.6	-7	-3	0.6	MILD ROP
87	B/O RATHINAM	F	LSCS	SINGLE	33	1500	HEART DISEASE	BIRTH ASPHYXIA, CPAP-2DAYS, O2HOOD-6DAYS, SEPSIS, HIE	-3.1	0	5.4	7.6	9.1	MILD ROP
88	B/O RAKKAMMAL	F	LSCS	SINGLE	32	1000	PIH	RDS,CPAP-3DAYS, O2HOOD-3DAYS, TRANSFUSION-PLT5,FFP1	-2.1	5.3	6.4	8.4	12.2	MILD ROP
89	B/O MURUGESHWARI THIRUMOORTHI	F	NVD	SINGLE	29	1000	-	BIRTH ASPHYXIA, CPAP-4DAYS, O2HOO-6DAYS, SEPSIS, HIE, TRANSFUSION-PLT3,FFP1	-14.5	-8.4	-6.1	-2.1	2.5	MILD ROP
90	B/O SUGANYA	F	NVD	TWIN	32	1400	-	RDS, CPAP-2DAYS, O2HOOD-7DAYS, HIE, SEPSIS	-33	-18.3	-11.7	-6.4	-4.5	MILD ROP

S.NO	NAME	SEX	DELIVERY MODE	SINGLE/ MULTIPLE BIRTHS	GA AT BIRTH (WEEKS)	BW (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	RELATIVE WEIGHT GAIN (g/kg/day)					RETINAL FINDING
									1st week	2nd week	3rd week	4th week	6th week	
91	B/O RAJESWARI	M	LSCS	SINGLE	33	1570	PIH	BIRTH ASPHYXIA, CPAP-2DAYS, O2HOOD-8DAYS, HIE	-9.3	-5.3	3.2	9.6	18.4	MILD ROP
92	B/O ASHTALAKSHMI	F	NVD	TWIN1	30	1300	-	RDS, APNOEA, O2-7DAYS, SEPSIS	-23.6	-15.4	-9.6	-4.7	-1.8	SEVERE ROP
93	B/O ASHTALAKSHMI	M	NVD	TWIN2	30	1300	-	RDS, APNOEA, O2-5DAYS, SEPSIS	-23.4	-13.1	-8.6	-3.8	-1.1	SEVERE ROP
94	B/O PANDISELVI	M	NVD	SINGLE	29	1150	-	MILD RDS, O2-1DAY, SEPSIS, TRANSFUSION-PL2, PDA	-20.5	-9	-6.6	-4	-1.4	SEVERE ROP
95	B/O SHARMILA	F	NVD	SINGLE	30	1250	-	APNOEA OF PREMATURITY, SURFACTANT, CPAP-4 DAYS, O2HOOD-3DAYS, SEPSIS	-17.6	-6.5	-6.8	-2.2	-1.6	SEVERE ROP
96	B/O AZHAGUTHAI	M	NVD	SINGLE	28	1050	PIH	RDS, CPAP-18DAYS, O2HOOD-4DAYS, TRANSFUSION-PLT5, WB1	-18.5	-6.4	-4.8	-3	-1.9	SEVERE ROP
97	B/O RAJESWARI MURUGAN	F	NVD	SINGLE	28	930	-	RDS, CPAP-1DAY, O2HOOD-10DAYS, SEPSIS, TRANSFUSION-PLT4	-13.3	-4.4	-4.1	-3.1	-1.1	SEVERE ROP
98	B/O SIVAPANDIYAMMAL	F	NVD	SINGLE	32	1200	-	RDS, SURFACTANT GIVEN, APNOEA, CPAP-3DAYS, O2HOOD-5DAYS, TRANSFUSION-PL2, ASD	-23	-14	-8.3	-2.9	-0.7	SEVERE ROP
99	B/O VAISHNAVI	F	NVD	SINGLE	30	1000	-	RDS, APNOEA, O2 HOOD-4DAYS, CPAP-2DAYS	-15.8	-7.4	-4.9	-2.1	0.6	SEVERE ROP
100	B/O SURYA	M	NVD	SINGLE	32	1300	-	RDS, SURFACTANT GIVEN, CPAP-5 DAYS, SIMV- 2DAYS, O2HOOD-5DAYS, SEPSIS, TRANSFUSION-PLT10, PC2, FFP4	-14.6	-6.9	-4.8	-2.2	0.2	SEVERE ROP

KEYS TO MASTER CHART

GA	GESTATIONAL AGE
BW	BIRTH WEIGHT
PIH	PREGNANCY INDUCED HYPERTENSION
RDS	RESPIRATORY DISTRESS SYNDROME
O_2	OXYGEN
CPAP	CONTINOUS POSTIVE AIRWAY PRESSURE
SIMV	SYNCHRONISED INTERMITTENT MECHANICAL VENTILATION
LSCS	LOWER SEGMENT CAESERIAN SECTION
NVD	NORMAL VAGINAL DELIVERY
HIE	HYPOXIC ISCHAEMIC ENCEPHALOPATHY
PLT	PLATELET
WB	WHOLE BLOOD
PC	PACKED CELL
FFP	FRESH FROZEN PLASMA
IVH	INTRAVENTRICULAR HEMMORHAGE
ASD	ATRIAL SEPTAL DEFECT
PFO	PATENT FORAMEN OVALE
PDA	PATENT DUCTUS ARTERIOSUS

ABBREVIATION

ROP	RETINOPATHY OF PREMATURITY
GA	GESTATIONAL AGE
BW	BIRTH WEIGHT
ET-ROP	THE EARLY TREATMENT FOR RETINOPATHY OF PREMATURITY
RLF	RETROLENTAL FIBROPLASIA
CRYO-ROP	CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY
LIGHT-ROP	THE EFFECT OF LIGHT REDUCTION ON RETINOPATHY OF PREMATURITY
VEGF	VASCULAR ENDOTHELIAL GROWTH FACTOR
IGF-1	INSULIN LIKE GROWTH FACTOR 1
CA	CHRONOLOGICAL AGE
PMA	POST MENSTRUAL AGE
NNF	NATIONAL NEONATOLOGY FORUM
ICROP	THE INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY
AP-ROP	AGGRESSIVE POSTERIOR POLE RETINOPATHY OF PREMATURITY
PHPV	PERSISTANT HYPERPLASTIC PRIMARY VITREOUS
BEAT-ROP	BEVACIZUMAB ELIMINATES THE ANGIOGENIC THREAT OF RETINOPATHY OF PREMATURITY
RD	RETINAL DETACHMENT
PUFA	POLY UNSATURATED FATTY ACID
Epo	ERYTHROPOIETIN
WINROP	WEIGHT IGF-1 NEONATAL RETINOPATHY OF PREMATURITY

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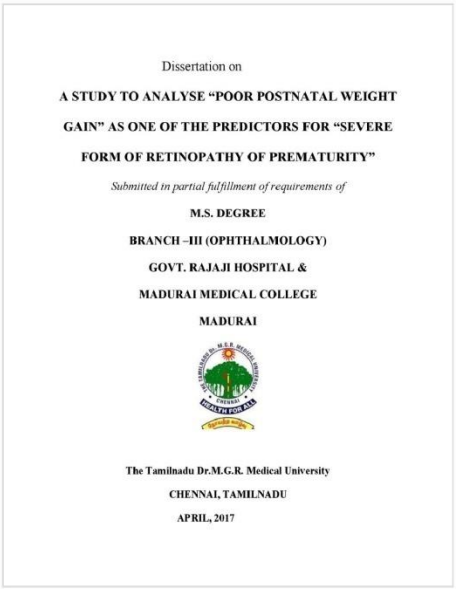

Dissertation on

A STUDY TO ANALYSE "POOR POSTNATAL WEIGHT GAIN" AS ONE OF THE PREDICTORS FOR "SEVERE FORM OF RETINOPATHY OF PREMATURITY"

Submitted in partial fulfillment of requirements of

M.S. DEGREE

BRANCH –III (OPHTHALMOLOGY)

GOVT. RAJAJI HOSPITAL &

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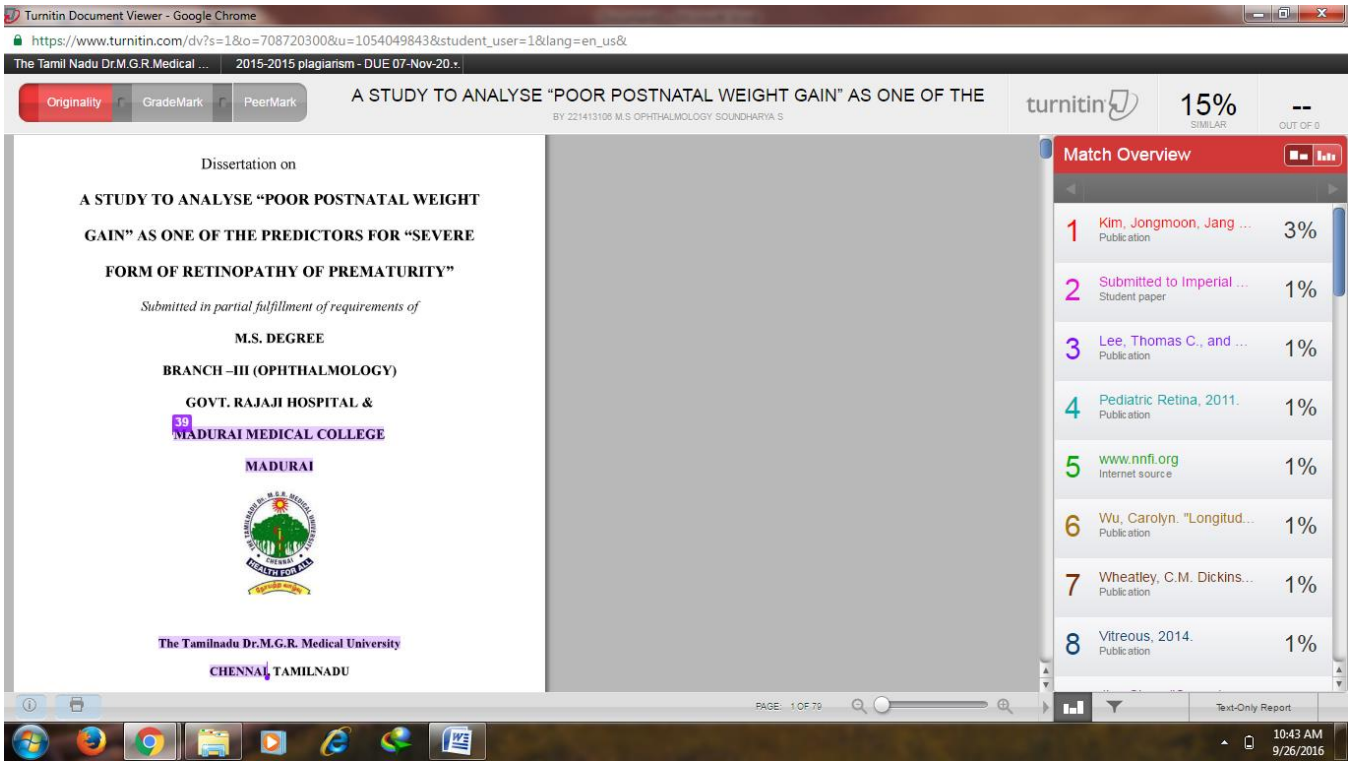
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